Cognitive development in children born preterm: Implications for theories of brain plasticity following early injury

MONICA LUCIANA

University of Minnesota, Minneapolis

Abstract

The human brain is functionally altered through experience, a phenomenon known as plasticity. Relevant experiences may be negative, as in brain injury. Adult brain injury results in permanent impairment. However, it has been assumed that early injury leads to substantial functional recovery. Animal studies suggest several predictions regarding whether this principle generally holds true. These studies indicate that the timing of brain injury, relative to the expected course of neurodevelopment, impacts the extent of recovery. Injuries occurring during the period of cell migration are particularly detrimental. However, outcome must be assessed longitudinally because apparent recovery in childhood may reverse as the brain matures. Moreover, recovery of one function may come at the expense of others. Whether these findings characterize outcome following preterm birth is the focus of this review. Preterm birth is associated with high rates of neurodevelopmental disability, primarily due to hypoxic–ischemic events. Periventricular brain structures and white matter tracts are particularly vulnerable to damage. Through school age, preterm children exhibit diminished levels of global intellectual function, attention, memory, and reasoning skills relative to full-term peers. It is questionable whether these deficits persist. Because few studies have followed recent cohorts into young adulthood, it is argued that outcome cannot be reliably described based on the available literature. Moreover, important contributors to later development have been neglected, including both genetic and experiential factors. With improved assessment, it may be possible to develop interventions based on the individual child’s constellation of genetic, biological, and sociodemographic risks.
before 37 weeks of the normal 40-week gestation (World Health Organization, 1977). Preterm birth of infants weighing less than 1500 g affects approximately 1.2% of live births annually in the United States, and rates have remained steady over the past decade (Volpe, 1998). Due to improvements in medical technology, survival rates for even the youngest preterm infants have improved from 44% in 1971 to approximately 85% currently (Hutton, Pharaoah, Cooke, & Stevenson, 1997; Volpe, 1998). However, despite increased rates of survival, rates of developmental disability in this population have not dramatically improved (Hack & Fanaroff, 1999). Between 5 and 15% of premature infants experience motor deficits consistent with cerebral palsy (Volpe, 1992). Additionally, 25–50% of preterm infants will experience later behavioral, academic, or cognitive problems that necessitate intervention (Volpe, 1998).

**Causes and Associated Features of Preterm Birth**

Preterm birth is a consequence of premature labor, which can be triggered by a number of factors. One of the most common causes is believed to be chorioamnionitis (inflammation of the protective membrane surrounding the fetus) or intrauterine infection that originates in the vaginal tract. A woman who experiences bacterial vaginosis between 23 and 26 weeks of gestation has a 50% increased risk of preterm delivery (Dammann & Leviton, 1997). A prepregnancy origin of the infection is possible, and the amniotic fluid is not necessarily affected (Goldenberg & Andrews, 1996). Preterm delivery might also be medically induced in cases of maternal hypertension or other health conditions such as pre-eclampsia (toxemia) that are life threatening to the mother or infant (Paneth, 1995, Taylor, Klein, & Hack, 2000). Other contributors include multiple births, which are becoming more prevalent in Western societies as a consequence of infertility treatments, smoking or drug use during pregnancy; poor maternal nutrition; and socioeconomic disadvantages such as low education, occupational status, and income. In one longitudinal study of preterm infants that was conducted in the Bronx, it was reported that one-third of families qualified for welfare assistance (Escalona, 1982). Rates of preterm birth also vary by race. In the United States, African American women are twice as likely as Caucasians to experience preterm labor and delivery (Taylor, Klein, & Hack, 2000), a vulnerability that may be an indirect consequence of poor maternal health or socioeconomic distress.

It should be stated at the outset that much of the current research on outcome following preterm birth focuses on neurobiological factors, minimizing the potential significance of concomitant features of the child’s lifestyle, such as poverty, which independently contribute to the child’s later cognitive and social development.

**Acute health consequences**

Although a substantial proportion of preterm infants are born small but otherwise healthy, others are extremely ill. A number of postnatal complications, not mutually exclusive, are routinely observed, and these include apnea (episodic cessations of breathing), respiratory distress, chronic lung disease, patent ductus arteriosus (a condition where the normal channel between the pulmonary artery and the aorta fails to close at birth), retinopathy (oxygen-induced damage to immature blood vessels in the retinae), necrotizing enterocolitis (severe inflammation of the intestinal system, resulting in cell death and digestive problems), septicemia (generalized systemic infection), seizures, and brain injury (Hack, Breslau, Weissman, Aram, Klein, & Borawski, 1991). Primary sensory handicaps in vision and hearing are common (Fazzi, Orcesi, Telesca, Ometto, Rondini, & Lanzi, 1997).

**Mechanisms of brain injury**

When brain injury occurs, it is frequently the result of one of two conditions, intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), each of which is associated with hypoxia or ischemia in the perinatal period (Volpe, 1998). Hypoxia refers to reductions in the oxygen supply to bodily tissues...
Cognitive development in children born preterm

Despite adequate perfusion of the tissue by blood, ischemia is a more severe low oxygen state that is usually the result of obstruction of the arterial blood supply or inadequate blood flow. An intraventricular hemorrhage is a hemorrhage of the area surrounding the lateral cerebral ventricles. The hemorrhage invades the lateral ventricles and can be classified into one of four grades of increasing severity (Papile, Burnstein, Burnstein, & Koffler, 1978). Grades 1 and 2 are considered mild in severity, whereas Grades 3 and 4 are more significant. Structures and pathways that are vulnerable to insult include the caudate nucleus, which parallels the shape of the lateral ventricles, the thalamus, the hippocampus, the optic radiations (which traverse this region to connect the thalamus with the occipital cortex), and the corpus callosum. The caudate nucleus is one of two structures that form the dorsal striatum. (The other striatal structure is the putamen.) The striatum is densely interconnected with the hippocampus, thalamus, and frontal cortex, forming several information processing circuits, each of which is devoted to a specific realm of behavior (Alexander, DeLong, & Strick, 1986). Because of these interconnections, the periventricular region is integral to information processing that is orchestrated by higher cortical association regions, such as the prefrontal cortex.

The periventricular area in premature infants is highly vulnerable to ischemic events due to the presence of arterial border zones in this region. These zones are particularly susceptible to drops in cerebral pressure or other alterations in cerebral blood flow (Volpe, 1992). There are a number of reasons for this physiological vulnerability, one of which is that systemically ill premature infants might experience a pressure-passive cerebral circulation, meaning that they lack the autoregulatory ability to compensate for changes in cerebral blood flow. Normally, cerebral pressure remains constant over a range of blood pressure changes, but in some premature infants, the cerebral arteries do not appropriately constrict and dilate in response to pressure variations. Due to the many systemic challenges facing the preterm infant, fluctuations in blood pressure are common, increasing the likelihood of ischemic episodes when pressure falls. PVL is caused by ischemia and refers to necrosis (death) of the white matter surrounding the lateral ventricles. Necrosis leads to the formation of cysts and to a process called gliosis. (In the context of central nervous system damage, outgrowths of glial cells enlarge to replace damaged tissue. This process is referred to as gliosis, and the resulting permanent scar tissue is called a plaque.)

During the third trimester of pregnancy, when preterm births are most likely to occur, glial cells in the periventricular region are in an active stage of differentiation into specialized subtypes, one of which is the oligodendrocyte. Oligodendrocytes are integral to the formation of the myelin sheath, an insulating layer surrounding neurons that dramatically increases the speed of nerve impulse conduction. Because gliosis interferes with the formation of oligodendrocytes, PVL disrupts myelination, causing cerebral atrophy, edema (swelling), and ventricular dilation (Taylor, Klein, & Hack, 2000; Volpe, 1992). PVL can result in either focal or diffuse white and gray matter damage. Affected structures can include the brainstem, basal ganglia, cerebellum, hippocampus, and/or frontal cortex (Baker, Stevenson, & Enzmann, 1988; Fuller, Guthrie, & Ellsworth, 1983; Ross, Tesman, Auld, & Nass, 1992). For reasons that are not entirely understood, males appear to be more vulnerable to the medical complications associated with prematurity than are females. This gender difference has been partially attributed to a lag of 1–3 weeks in cerebral and pulmonary maturation in boys relative to girls (Lauterbach, Raz, & Sander, 2001; Raz, Lauterbach, Hopkins, Glogowski, Porter, Riggs, & Sander, 1995).

Until recently it was thought that brain injury in the preterm infant was a peri- or postnatal event triggered by episodes of hypoxia or ischemia. Current models have expanded upon this view to suggest that neural injury may also be related to the immunological response of the mother to intrauterine infection (Dammann, Kuban, & Leviton, 2002; Duggan, Maalouf, Watts, Sullivan, Counsell, Allsop, Al-Nakib, Rutherford, Battin, Roberts, & Edwards, 2001; Hitti, Tarczy–Hornoch,
Murphy, Hillier, Aura, & Eschenbach, 2001; Leviton, 1993; Toti & DeFelice, 2001). This model is based on a view of the mother and fetus as an integrated neurophysiological unit, of which the uterus, the fetal circulation, and the fetal brain are three components (Dammann & Leviton, 1997). The placenta links the uterus and the fetal circulation, whereas the fetal circulation and fetal brain are linked by the fetal blood brain barrier. In the context of maternal infection, proinflammatory substances called cytokines are released by the mother’s immune system into her circulation and can cross the circulatory boundaries between her and the fetus. In the course of gestation, cytokines can provoke alterations in fetal brain circulation. Through a complex cascade of events, these alterations can result in intraventricular hemorrhage and subsequent cerebral edema, which concentrates blood and cytokines in the ventricular region via cerebrospinal fluid. Within the ventricles, cytokines have toxic effects on developing white matter (Leviton, 1993). This model may explain why some infants are more vulnerable to PVL and associated cerebral damage than others, because it will be those infants who mount a proinflammatory response in utero who will be at highest risk for cerebral lesions (Duggan et al., 2001). Notably, this model has profound implications for prevention and intervention strategies, because it implies that damage begins in vulnerable infants prior to birth.

Predictors of outcome

Longitudinal studies suggest that one of the most reliable predictors of neonatal and longer term outcome is birth weight, so within this literature, it is conventional to divide infants into those with extremely low birth weight (ELBW, <750 g, 1.6 lb), very low birth weight (VLBW, 750–1499 g, <3.3 lb), and LBW (1500–2500 g, <5.5 lb). Ongoing studies suggest that outcomes are worst for ELBW (Taylor, Klein, & Hack, 2000). A related predictor is gestational age, although the onset of pregnancy can be difficult to precisely determine based on mothers’ self-reports of their menstrual histories. Typically, gestational age and birth weight are positively correlated, although this is not always the case. Infants who are small for gestational age have likely experienced prenatal physiological stress due to maternal malnutrition or placental insufficiency (Georgieff & Rao, 2001). Prior to 1990, survival of infants born before 24 weeks of gestation or weighing less than 750 g was rare (Hack, Friedman, & Fanaroff, 1996), but because of improved neonatal care, 24 weeks is now the accepted age of viability.

The course of neonatal treatment also influences later development. Taylor, Klein, and Hack (2000) describe three eras in the treatment of preterm infants. During the first era, from the early 1900s to the 1940s, life-support technologies were unavailable and treatments were conservative. Very few extremely premature infants survived. During the second era, from the 1940s to 1960s, treatment strategies included the use of supplemental oxygen, antibiotics, and nutritional alterations, each of which, although well intentioned, was associated with a specific type of morbidity. Overuse of oxygen led to retinopathy and subsequent blindness; antibiotics were associated with deafness; and nutritional interventions (or lack thereof) resulted in malnourishment. Infants who survived in this era have been described as having poor neurological and cognitive outcomes. The modern era of neonatal intensive care treatment began in the 1960s and is characterized by improvements in obstetrical care, provision of assisted ventilation, cardiovascular monitoring, intravenous fluids, provision of parental nutrition, and treatments directed at specific conditions associated with prematurity (Taylor, Klein, & Hack, 2000). For example, laser surgery is now used to treat retinopathy early in its manifestation, and respiratory status is continuously monitored in infants who are predisposed to apnea. Surfactant therapy to treat immature lung development was instituted in 1980 (Curley & Halliday, 2001). Treatment cohort effects are important to consider when evaluating this literature, because although it is the case that neonatal interventions have increased survival rates in preterm infants, these interventions are not always be-
Cognitive development in children born preterm

whether these environmental challenges can be viewed as benign, enriched, or detriments to development is an empirical question that can be investigated in healthy preterm infants.

Second, if brain injury is apparent following a preterm birth, several issues are pertinent to the course of later development. Among these are the timing of the injury (whether it occurred prenatally, during birth, or postnatally), what exactly went wrong (e.g., hypoxia, intraventricular hemorrhage, seizures), and behavior postinjury, which must be evaluated prospectively in the context of knowledge regarding normative patterns of brain and cognitive development. Several developmental courses are possible, and all have been observed in the context of animal studies of early brain damage (Kolb, 1995). In the first trajectory, damage is so severe that development may be hampered early on but seems to improve with increasing age, suggesting recovery of function. The fourth possibility, termed “growing into injury,” is one in which evidence of cognitive dysfunction may be subtle or even absent in infancy but becomes more evident with increased age. This type of late-emerging cognitive dysfunction has been termed a “sleeper effect” (McGrath, Sullivan, Lester, & Oh, 2000).

The first pattern is minimally informative, because it is logical to expect that severe damage would lead to severe dysfunction. Neural plasticity is only possible if enough of the necessary “hardware” remains uncompromised after injury. In contrast, the latter three patterns are more remarkable in the degree to which they enhance our knowledge of brain plasticity. Which one prevails depends on when and where the brain damage occurred. However, to complicate matters, some evidence from animal studies suggests that functional deficits, when considered from a lifespan perspective, may not be evident until old age, because the early-injured brains may be more vulnerable to degenerative processes (Kolb, 1995). Thus, because of the ongoing
dynamics of neural function, brain development may never be complete or static. For this reason, “outcome” is likely to fluctuate and cannot be defined by description of an individual’s functioning at a single point in time. A seemingly poor outcome at one phase of development may initiate a cascade of social and biological events that will impact later functioning. Similarly, good adjustment during critical periods may be protective in the context of later adversity. Thus, the challenge is to describe the consequences of early brain injury in a continuously developing individual with an awareness of what is expected in terms of normative functional progress in childhood and adaptability in adulthood.

The Normative Sequence of Early Brain Development

Prior to a discussion of human outcome studies, steps in the normative sequence of brain development will be briefly reviewed. The mammalian brain, including that of the human, develops according to a generally invariant sequence, much of which is intrinsically programmed by genetic factors (Goldman–Rakic, Bourgeois, & Rakic, 1997). The early nervous system begins as a hollow tube that surrounds a single ventricle. The area that lines the ventricle is referred to as the proliferative zone. Neural stem cells reside in this area and divide either symmetrically to produce two stem cells or asymmetrically to produce a stem cell and a progenitor cell. Neurons and glia are derived from progenitor cells, a process known as neurogenesis (Kolb & Gibb, 2001). As neurons are formed, they migrate to fixed destinations within the early-developing cortex in an inside-out fashion. That is, cells that comprise the inner layers of the six-layered cortex are placed first, followed by those that reside in the outermost layers. It is believed that cell proliferation is largely complete by the fifth month of gestation. Migration continues for several more months. Most neurons migrate to their final destinations along filaments known as radial glial fibers (Rakic, 1972), which disappear after migration is complete. Having reached their targeted destinations, neurons undergo the process of differentiation and synaptic maturation. Synaptic maturation includes the growth of dendritic processes and axonal projections, myelination, synaptogenesis, and synthesis of neurochemicals.

In the human, dendritic growth begins in the deepest cortical layers during the seventh prenatal month. (Dendrites are the treelike extensions emanating from neuronal bodies that receive input from other cells, and dendritic spines are specific contact points). The time of maximal dendritic growth and synaptogenesis occurs from roughly 8 months postnatal to 2 years. During this time, an excess of synaptic connections form. Later in childhood, selective pruning eliminates this excess and it is not completed in areas such as the frontal cortex until some time after puberty (Kolb, 1995). Thus, the synaptic architecture that characterizes any one individual’s brain does not stabilize until young adulthood.

The overproduction of synapses early in life and the selective elimination of excess connections in adolescence allows experience to modify synaptic architecture. Whereas some aspects of experience (e.g., visual stimulation, independent locomotion) are expected to characterize the lives of all people, others are uniquely determined by the quality of an individual’s immediate environment. These unique experiences underlie individual differences in affective and cognitive development via synaptic alterations. These alterations are not unlimited in potential but occur within a reaction range determined by the individual’s genetic endowments (Collins & Depue, 1992). Thus, to some extent, synaptic “excess” is a relative term that may vary between individuals, and pruning is believed to operate according to a “use it or lose it” principle. Therefore, it is expected that with age, the quality of postnatal experience will exert an increasingly detectable influence on an individual’s synaptic structure.

This sequence of events appears to be similar across mammalian species, but its timing varies. At birth, species differ considerably in terms of where they are in the sequence. For example, in the human, migration is virtually complete at birth and synaptogenesis is in progress. In contrast, the rat is born after a 3-
Cognitive development in children born preterm

week gestation, and neuronal migration takes place during the first postnatal week. Thus, at birth, a rat is equivalent to a 5-month-old (preterm) human fetus, whereas a human at birth is equivalent to a 5-day-old (postnatal) rat (Kolb, 1995). These relationships must be understood in order for the literature on experimentally induced early brain injury to be evaluated. Instead of deriving cross-species conclusions based on the age of the animal (e.g., inferring similarities between different species of laboratory animals at birth), comparisons should be made between corresponding periods in the sequence of brain development (e.g., studying different species’ behavior during similar phases of neurodevelopment).

Theories of Plasticity Following Early Brain Damage

One commonly held principle, referred to as the Kennard principle, holds that outcome is more favorable after early versus adult brain injury (Kennard, 1942). Kennard observed that infant monkeys with unilateral motor cortex lesions appeared to experience better outcomes than adult animals with similar lesions, a finding that she attributed to changes in cortical organization. Simply put, the young brain was presumed to cope more flexibly with injury because its development was in a state of flux. Although the Kennard principle is intuitively appealing, two limitations have been discussed (Kolb, 1995). The first is that it is often invoked without qualification. This is a problem, because the extent to which a developing brain is able to compensate for early injury will depend on when, during the maturational sequence outlined above, the injury occurs. A related second problem is that the Kennard principle may be illogical in some respects. Kolb (1995) compares the process of brain development to that of building a house. In order to remain structurally sound, the house must be framed on a sturdy foundation. No amount of cosmetic improvement will compensate for an inadequate foundation, and problems will be apparent with increasing age. This alternative view, championed by Donald Hebb, suggests that brain damage early in life may actually be worse than later damage, because it prohibits expected neural organization and behavioral development from occurring (Hebb, 1947, 1949). Thus, Kennard’s model assumes fewer restrictions on the potential for recovery after early injury than does Hebb’s, a debate that has also been framed around viewing brain plasticity from a probabilistic versus causal epigenetic perspective (Johnson, 1999). Animal models of early brain injury have been useful in delineating areas of compromise between these theories (Kolb & Gibb, 2001). These models also permit the derivation of hypotheses regarding outcomes following neonatal injuries in human infants.

Animal models of early brain injury

Rat models. As mentioned above, in terms of brain development, rats at birth are equivalent to human fetuses in the second trimester of pregnancy. At 5 days postnatal, rats are equivalent to newborn human infants; at 7–8 days postnatal, the rat is equivalent to a 1-month-old infant. Thus, we can compare the effects of damage to the early-developing rat brain at these time points to model prenatal versus early postnatal injury in the human. Much of the research on this topic has been conducted in Bryan Kolb’s laboratory and has focused on the effects of frontal lobe lesions. This literature will be emphasized. Lesions of frontal lobe structures in adult rats invariably result in profound behavioral deficits. In contrast, Kolb and colleagues have reported that across a variety of behavioral tasks, adult behavior is normal in rats subjected to frontal lobotomies at age 7 days (Kolb & Nonneman, 1976, 1978). Similar findings are observed in 10-day-old rats. However, earlier lesions, occurring when the animals are 5 days old or younger, result in later deficits that are worse than if the animals were lesioned in adulthood (Kolb, 1987; Kolb & Whishaw, 1981). Deficits have been observed on measures of skilled reaching behavior and spatial navigation, two critical aspects of rodent cognition. A similar developmental pattern is observed with posterior lesions (Kolb, Hewson, & Whishaw, 1993). When these effects are mapped onto what is known about brain development in the
rat in the first 2 weeks of life, they suggest that injury occurring during the period of cell migration or early synaptogenesis (<5 days) is particularly detrimental to later functioning. In contrast, injury that occurs later in the course of synaptogenesis (~7–10 days) permits a substantial degree of recovery (Kolb, 1995). However, later lesioned animals show deficits in species-typical behaviors such as food hoarding, claw trimming, and nest building when they reach adulthood. Given that species-typical behaviors are likely to be subcortically mediated, it may be that the mechanisms permitting recovery are detrimental to other unpredicted aspects of neural function. Therefore, recovery should be evaluated in relation to a broad range of behaviors.

Other general features observed in these studies are that large or bilateral lesions produce more severe deficits than more restricted or unilateral lesions. Additionally, animals with early lesions exhibit relatively small brain volumes and thinner cortical mantles, both more pronounced in the area of injury. Because brain size does not necessarily correlate with level of function (Kolb & Whishaw, 1981), organizational changes such as synaptic number, cortical connectivity, and neurogenesis have also been assessed.

**Synaptic number.** The number of functional synapses in a region of brain tissue can be estimated by examining a neuron’s degree of dendritic arborization and its number of dendritic spines. The cortical neurons of rats that experienced lesions at birth consistently show a general atrophy of dendritic arborization as well as a decline in spine density across the cortical mantle (Kolb & Gibb, 2001; Kolb, Gibb, & van der Kooy, 1994). In contrast, animals with later lesions, who experience better recoveries, show increases in dendritic arborization and spine density.

**Cortical connectivity.** The corticospinal motor pathway is ipsilaterally organized at levels above the brainstem. Rats and cats that undergo unilateral motor cortex lesions, similar to those induced by Kennard (1942), exhibit significant expansions of the corticospinal pathway from the undamaged hemisphere. This expansion, although aberrant, is thought to reflect a compensatory failure of pruning of connections that would typically be discarded during development. Consistent with the Kennard effect, it is correlated with partial recovery of forelimb use (Kolb & Gibb, 2001; Whishaw & Kolb, 1988). However, this anomalous pattern of connectivity is not without adverse consequences. Rats that are lesioned at a young age show greater enhancement of their undamaged corticospinal connections, but relative to later lesioned animals, they are not the animals with the best outcomes. They exhibit unexpected cognitive deficits on tasks that would not typically require the motor cortex, suggesting that the atypical connections form and function at a cost to other cortical regions (Kolb, Cioe, & Whishaw, 2000a, 2000b).

**Neurogenesis.** In select regions of the rat brain, notably the medial frontal cortex and olfactory bulb, neurogenesis appears to be reactivated after lesions on postnatal days 7–12, leading to a significant, although not complete, functional recovery. However, again, this plasticity may come at some price. When ventricular stem cells are removed from these animals and placed in vitro with neurotrophic factors (which would normally provoke rapid cell division), few new cells are formed (Kolb & Gibb, 2001). The long-term implication of this finding is unclear, but it suggests that the regeneration of new tissue after early injury limits the later proliferative potential of ventricular stem cells.

Finally, mechanisms of recovery appear to operate throughout the developmental period, such that the full extent of recovery cannot be determined until after the period of synaptic pruning has ended. For example, rats subjected to frontal lesions on days 1 and 10 both exhibit deficits in the Morris Water Maze task of spatial navigation when they are tested at day 19. However, in adulthood (at day 56), the day-10 lesioned group tests normally whereas the day-1 lesioned group continues to demonstrate impairment (Kolb, 1995).

In summary, this work suggests that outcome following early brain injury may change bidirectionally as development proceeds. In
addition, a number of neural mechanisms may promote recovery of functions that are immediately dependent on lesioned areas. However, other seemingly unrelated behavioral functions may be impaired later in development.

**Monkey models of early injury.** In contrast to rats and humans, monkeys are born embryologically late in brain development, limiting the extent to which primate studies can model human preterm birth. A 10-day-old rat is equivalent to a 1-month-old human infant who is equivalent, in turn, to a prenatal monkey. In the prenatal monkey, neuronal migration occurs from day 69 to day 135 of an average 165-day gestation (Goldman–Rakic, 1987b), so injuries during this time period would be expected to adversely affect later behavior. Goldman and Galkin (1978) prenatally ablated the dorsolateral prefrontal cortex in monkeys between prenatal days 102 and 119. Counter to expectation, these animals performed in a manner that was indistinguishable from control animals on measures of frontal lobe function as they matured. Later dissections indicated that a compensatory reorganization of thalamocortical connections had altered the gross morphological characteristics of the cortex.

In contrast, Goldman and Rosvold (1972) lesioned the head of the caudate nucleus in a group of 10 infant rhesus monkeys, comparing their later development to (a) unoperated infant controls, (b) monkeys with caudate lesions made in the juvenile period, and (c) unoperated juvenile controls. Lesions were made bilaterally to the anterodorsal sector of the head of the caudate nucleus, because this region receives a direct projection from the dorsolateral prefrontal cortex (PVC; Johnson, Rosvold, & Mishkin, 1968). After a 10-month postoperative interval, monkeys were tested on a battery of behavioral tasks that included measures of spatial delayed response, visual pattern discrimination, spatial delayed alternation, and object discrimination/reversal. Spatial delayed response and alternation are sensitive to dorsolateral PFC damage in adult animals (Goldman-Rakic, 1987a) but they would be expected to be susceptible to caudate lesions, given the extent to which the frontal cortex and striatum are interconnected. Although the behavioral responses to small lesions were variable across individual animals, the effects of large lesions were uniform. In both the juveniles and infants, the caudate-lesioned monkeys were impaired on both spatial delayed response and alternation relative to age-matched controls. Performance on the visual pattern recognition and object discrimination tasks was unimpaired. These findings are similar to the effects of caudate lesions made in adult animals, suggesting that functions dependent upon the caudate nucleus are particularly vulnerable to the effects of early injury.

Similar behavioral effects are evident in adult animals with prefrontal lesions, indicating that early injury to the caudate is behaviorally manifested in infancy and childhood as frontal lobe impairment. Counterintuitively, when the dorsolateral PFC is removed at these same ages, infant and juvenile monkeys are unimpaired on the spatial delayed response and alternation tasks during childhood (Goldman, 1971). This finding might be interpreted as evidence of neural plasticity. However, when the early PFC-lesioned monkeys are retested at 24 months of age (corresponding to late adolescence in the human), they are impaired on the spatial delayed response and alternation tasks relative to peers (Goldman, Rosvold, & Mishkin, 1970).

Therefore, the important conclusion to be drawn from these studies is that the lack of deficits observed at early ages in the PFC-lesioned animals is a function of immaturity and not the result of neural plasticity, which might have been assumed in the absence of a longitudinal assessment (Goldman & Rosvold, 1972). Moreover, executive functions that are orchestrated by the PFC in adulthood may be mediated by the caudate nucleus during childhood. As the individual matures, the caudate loses autonomous control over these behaviors as they are transferred to the PFC (Goldman & Rosvold, 1972). By extension, and this is a critical point, executive function deficits observed in human children are more likely to be due to subcortical (striatal) damage than to prefrontal injury, because, as described above,
early injury to the prefrontal cortex does not manifest itself in behavior until adulthood. In contrast, the effects of striatal injuries are evident in childhood, and the caudate is highly vulnerable to hypoxia and ischemia. To determine if the PFC has been specifically damaged, behavior must be observed in adulthood.

Predictions for human studies

Based on these controlled experiments, several predictions can be made regarding outcomes in human infants who experience neurologic challenges in the neonatal period.

First, infants born during the third trimester of pregnancy, when neural migration is in progress, will experience poor cognitive outcomes relative to infants born later in gestation. Second, neuroimaging may indicate that overall brain volumes are decreased in these infants. Regional analyses will indicate that vulnerable areas of injury include periventricular structures, the hippocampus, the striatum, and the frontal cortex. Functions attributed to those areas that reach full functional maturity early in life (e.g., hippocampus, caudate nucleus) will be impaired in childhood. Executive functions may be particularly vulnerable.

However, this vulnerability may be more subtly manifested in adulthood if an intact PFC assumes control over these functions. Third, evidence of substantial neural damage in the neonatal period will remain stable over time, because plasticity will be limited. But in children with more moderate or mild indications of neural abnormality, outcome must be considered from a lifespan perspective. Measures of cognitive functions that are dependent upon late-maturing regions (e.g., the frontal cortex), when administered in childhood, may or may not predict levels of performance in young adulthood.

The sequence of normal human brain development and expectations regarding recovery following early brain injury are summarized in Figure 1.

Neurobehavioral Development of Preterm Human Infants

There are obvious methodological constraints in evaluating these predictions in preterm infants. Although laboratory studies make it possible to equate the levels of brain development across species at the time of an injury, experiences are not equivalent. Thus, the preterm human infant who is born at a time when neural migration is not yet complete, unlike the rat, must also cope with a constellation of extraterine experiences for which it is ill-prepared. Moreover, the precision and location of neural damage is reasonably well controlled in laboratory studies but is unpredictable in the human. Finally, conclusions regarding functional recovery rely on the extent to which behavioral functions are broadly and validly assessed.

One assumption guiding interpretations from prospective studies is that the measurement of functional deficits is consistently valid from birth through childhood and into adulthood. This is not necessarily the case, and within most longitudinal studies, assessment tools (even those that purportedly measure the same construct) vary markedly as development proceeds. Measures of infant development are understandably limited due to the child’s inability to assist in the assessment process. In the absence of a gross abnormality, most judgments regarding functional progress are based on whether the child has achieved basic behavioral milestones at the appropriate time and/or how the child performs on measures of ability, such as the Bayley Scales of Infant Development (Bayley, 1993). Because such scales rely heavily on motor skills, they may not be sensitive to cognitive deficits that appear to emerge suddenly at school-age. The extent to which this measurement difficulty confounds longitudinal research is unclear, and it is questionable whether infant measures of cognition can be substantially improved.

With that caveat in mind, if we assume that infant measures of physical and cognitive development are valid, then most evidence suggests that between infancy and school age, children are more likely to grow into, than to grow out of, deficits following premature birth.

Infancy

Brain imaging of preterm infants soon after birth indicates a high prevalence of neural in-
Figure 1. Plasticity in relation to stages of neurodevelopment. In the human, brain development proceeds in a sequence, as described in the text. This sequence begins with neurogenesis and ends with synaptic pruning. Following early brain damage, plasticity varies according to when the injury took place in the sequence. Animal studies suggest that plasticity will be very low during the period of cell migration, corresponding to the second and third trimesters of pregnancy (second panel) and during adulthood (last panel) when synaptic networks have stabilized. Plasticity will be highest prior to synaptic stabilization during early and middle childhood (third panel; adapted from Kolb, 1995).
jury that becomes more pronounced during the early neonatal period. Because it is amenable to bedside assessment, ultrasonography has been the measurement technique of choice since the late 1970s (Stewart, Rifkin, Amess, Kirkbridge, Townsend, Miller, Lewis, Kingsley, Moseley, Foster, & Murray, 1999), but some researchers have recently capitalized upon the increased resolution of magnetic resonance imaging (MRI). Maalouf, Duggan, Rutherford, Counsell, Fletcher, Battin, Cowan, and Edwards (1999) used MRI to obtain brain images in preterm infants and term controls shortly after birth. Infants were then imaged serially until the preterm infants reached forty weeks of postconceptional age. A number of abnormal findings indicative of cerebral atrophy and white matter damage were evident in the preterm sample. For example, 37% of preterm infants exhibited ventricular dilation neonatally. Of these, 60% had intraventricular hemorrhages. At term, 71% of these infants were rescanned, and 76% showed evidence of ventricular dilation. Eighty-three percent showed squaring of the margins surrounding the lateral ventricles, particularly at the anterior horn. Additionally, on their initial scans, 17% of preterm infants had unequivocal evidence of white matter lesions, while another 20% exhibited diffuse and excessive high signal intensity (a marker of possible white matter disease) in subcortical regions. After repeat MRI, 62% had findings consistent with white matter abnormalities. Thirty-eight percent had evidence of interhemispheric widening, suggesting damage to the callosal fibers that link the two hemispheres, most prominent in frontal regions. Twelve percent of preterm infants had striatal lesions on initial scans, and this number remained stable at the term follow-up. Because many preterm infants exhibited brain abnormalities so soon after birth, these data support the view that white matter injury begins prenatally and becomes progressively worse during the neonatal period.

Huppi et al. (1996) compared healthy preterm infants to matched controls. The preterm infants were tested 1–3 weeks after birth and again at term. Using MRI to describe brain development in the preterm group, the authors reported significant increases in gray–white matter differentiation as the infants matured. These changes were accompanied by significant indications of behavioral maturation in areas such as motor function, attention, and self-regulation. Preterm infants were also compared to term controls when the former group reached forty weeks of postconceptional age. This comparison indicated that the premature infants, while demonstrating a significant degree of brain development over time, nonetheless exhibited less gray–white matter differentiation and a less advanced stage of myelination than the control infants. Moreover, performance in four of six behavioral domains lagged in the premature infants, suggesting that the delays in brain development were paralleled in behavior. Since the preterm infants in this study were healthy, these findings address the merits of the intrauterine versus extrauterine environment on patterns of neurodevelopmental growth. They suggest that even healthy preterm infants are at risk for maturational delays.

Indeed, a common finding in studies of preterm infants is that performance on gross indices of neurobehavioral function, such as the Bayley Scales of Infant Development (Bayley, 1993), declines from the first to the second year of life (Escalona, 1982; Resnick, Strailka, Carter, Ariet, Bucciarelli, Furlough, Evans, Curran, & Ausbon, 1990; Wallace, Rose, McCarton, Kurtzberg, & Vaughan, 1995; Weisglas-Kuperus, Baerts, Smrkovsky, & Sauer, 1993). Several specific abilities also appear to be compromised, one of which is visual attention as measured by infants’ looking times to novel versus familiar stimuli (Rose, Feldman, McCarton, & Wolfson, 1988). At 7 months of age, VLBW preterm infants require a longer stimulus exposure time to become familiar with novel objects. Between 5 and 12 months of age, these infants also exhibit longer fixation times and a decreased tendency to shift attention between visual stimuli (Rose, Feldman, & Janowski, 2001), suggesting slower speeds of information processing and difficulties in efficiently allocating their attentional resources to visual cues. Notably, these problems contribute to apparent deficits in recognition memory, as evidenced by the lack of a novelty preference in
visual paired-comparison paradigms. However, additional manipulations have revealed that these deficits are not due to poor memory retrieval but are instead based on the inability to encode visual information in a developmentally appropriate length of time.

Delays in the development of gross and fine motor skills are also normative within this population (Goyen, Lui, & Woods, 1998), and at least one study has reported deficits in preterm infants’ abilities to reproduce explicitly learned motor sequences (de Haan, Bauer, Georgieff, & Nelson, 2000). In this study, healthy preterm infants born before the 34th week of gestation were compared to a group of full-term controls and to a second group of preterm infants born between 35 and 37 weeks of gestation. All infants were studied during their second years of life on an elicited imitation procedure (Bauer & Hertsgaard, 1993; Meltzoff, 1995). In elicited imitation, memory for individual events and for their temporal order is assessed by presenting infants with an action sequence and allowing them to imitate it, both immediately and after a delay. The individual events that form the sequences vary in whether they can be logically linked or whether they are arbitrary. The three groups were equivalent in their ability to remember individual actions, but they differed in their ability to remember the actions in the correct order regardless of whether they were tested immediately or after a delay. Additionally, when the to-be-remembered sequences were arbitrary, premature infants did not recall them at above chance levels of accuracy. Consistent with Rose’s finding of poor attentional efficiency in preterm infants (Rose, Feldman, McCarten, & Wolfson, 1988; Rose et al., 2001), this finding suggests that as toddlers, premature infants benefit from the provision of increased structure in encoding visuomotor information.

Because the elicited imitation paradigm requires explicit memory as well as memory for temporal order, it may recruit both hippocampal and frontal lobe based memory systems. The hippocampus and surrounding structures are known to mediate explicit memory processes (Nelson, 1995), while the ability to procedurally recall items in their correct sequence (Knopman & Nissen, 1987) as well as the ability to make decisions about the temporal order of events (Milner, Corsi, & Leonard, 1991) are dependent upon frontostriatal structures. Thus, the findings of deHaan et al. (2000) suggest that even very healthy preterm infants may exhibit deficits in executive functions as these skills are beginning to emerge in development. Similarly, Ross, Boatright, Auld, and Nass, (1996) reported impaired spatial working memory abilities in 2-year-old preterm children with histories of intraventricular hemorrhage. Like the learning of motor sequences, spatial working memory is a putative frontal lobe function that may, as the animal work suggests, rely on the integrity of periventricular striatal structures early in development (Goldman & Rosvold, 1972).

It was also noted by de Haan et al. (2000) that the ability to perform arbitrary elicited imitation sequences correlates in healthy children with the development of language skills. Notably, preterm children have a high rate of speech therapy utilization (Taylor, Klein, & Hack, 2000; Tideman, 2000), with most deficits in the area of expressive, but not receptive, language. High-risk subgroups that have experienced chronic lung disease or IVH have decreased levels of social initiation, less frequent speech, and an increased rate of inappropriate responses when interacting with their mothers (Landry, Chapieski, Richardson, Palmer, & Hall, 1990). As compared to term-born children, they appear to be more dependent upon caregivers to provide structure in social interactions (Landry, Smith, Miller–Loncar, & Swank, 1998). These delays in expressive language acquisition are also consistent with deficient frontostriatal functioning, because fluency is mediated by a network of structures that includes Broca’s area in the lateral frontal cortex (Goldman–Rakic, 1987b).

Several groups have considered the extent to which deficits in the infancy period persist into early childhood, and much of this work has focused on neurological status. In one study, VLBW infants with a mean gestational age of 29 weeks were classified according to ultrasound scans obtained in the neonatal period into one of two groups (Fazzi et al., 1997). The first group was characterized by
infants with normal scans or with evidence of uncomplicated intraventricular hemorrhage. The second group included infants with parenchymal lesions or complicated hemorrhages. The infants were subsequently retested at ages 24 months and 5–7 years. Neurological status was assessed at each time point. Analysis of the combined sample revealed that at 24 months of age, only 55% of the preterms were described as normal, whereas 25% had minor sequelae and 20% had major sequelae. At 5–7 years of age, a general decline in status was evident for children previously classified as normal. At this time, 31% were described as normal, 49% exhibited minor sequelae, and the same 20% of children exhibited major neurological consequences of their preterm births. Major sequelae included symptoms consistent with cerebral palsy. Minor sequelae included tone and reflex abnormalities or asymmetries.

Within Group 1, there were no cases of major long-term sequelae. However, 42% of children who were described as normal at 24 months of age were described as having minor abnormalities at ages 5–7 years. Within Group 2, 60% of children described as normal at 24 months were classified as having minor sequelae at ages 5–7. Thus, when major sequelae were identified early, these tended to remain stable over time. However, a “normal” classification in infancy was a relatively poor predictor of later functioning, because minor neurological abnormalities became increasingly evident as preterm children approached school age. In terms of cognitive functioning at age 5–7 years, both groups exhibited deficits in quantitative and motor skills relative to their verbal abilities as assessed by the McCarthy Scales’ Global Cognitive Index (McCarthy, 1970).

Dewey, Crawford, Creighton, and Sauve (2000) similarly classified children of VLBW at age 3 years as either “developing normally” or “suspect.” At age 6–14 years, they were compared to an age-matched control group on a parent report of everyday cognitive abilities. Parents rated VLBW children as more difficult and more inclined to experience school difficulties. Because parental report may not be an objective measurement of children’s abilities, it is also important to note that these authors administered a battery of standardized neuropsychological tests. Findings indicated that both VLBW groups differed statistically from the control group on measures of IQ, motor function, language skill, and school achievement. In addition, it was reported that children classified as suspect at age 3 differed from controls and from the developing normally VLBW group on a range of neuropsychological functions (Dewey, Crawford, Creighton, & Sauve, 1999). They were particularly impaired on measures of motor skill, visuomotor integration, and memory. In contrast, the developing normally group displayed relative deficits only on visuomotor and motor tests. Both groups of premature infants had lower Wechsler Intelligence Scale for Children—III (WISC-III; Wechsler, 1991) IQ scores than children in the term control group. The authors suggest that the nonspecific impairments observed in VLBW children classified as suspect are the result of diffuse patterns of neural damage. However, when damage is less severe, as in the VLBW “developing normally” group, focal deficits in motor functions are a likely result.

To summarize, studies of preterm children in the infancy period provide evidence of cerebral atrophy and white matter damage on brain scans. These infants tend to be significantly delayed in global abilities (Escalona, 1982; Fazzi et al., 1997; Huppi et al., 1996; Ross et al., 1992; Wallace et al., 1995), with particular emphasis on delayed motor development. These deficits persist into the preschool age period. These studies generally indicate that preterm children differ cognitively from full-term controls in a statistical sense. However, whether these statistically significant differences are clinically meaningful in children who do not present with major neurological injury is equivocal. It may be that general cognitive abilities are compromised because of inefficiencies in information processing and a lack of ease in encoding visual information (Rose et al., 1988, 2001). Both hypotheses would be consistent with white matter disease and can be difficult to detect behaviorally. From a neurological standpoint, whereas evidence of major neurological prob-
Cognitive development in children born preterm

Problems (e.g., cerebral palsy) is a strong prognostic indicator regarding future functioning, normal neurological function in early infancy is unreliable as a predictor of later behavior. Indeed, the trend is for neurological status to decline from infancy to school age.

Preschool to school age

Functioning in the preschool and school age periods is unequivocally related to the level of medical risk experienced by the child neonatally (McGrath et al., 2000; Taylor, Klein, & Hack, 2000). Children with the highest levels of medical risk in the neonatal period and/or those with birth weights under 1000 g tend to be those who function most poorly across behavioral domains. They are also more likely than term-born children to experience chronic health problems, such as asthma, respiratory infections, and visual problems that limit activities of daily living (Hack, 1999). A number of researchers have reported that preterm children are more likely than full-term children to encounter academic difficulties, including poor academic achievement, placement in special education, and repetition of a grade (Halsey, Collins, & Anderson, 1996; Klebanov, Brooks–Gunn, & McCormick, 1994; Klein, Hack, & Breslau, 1989; Luciana, Lindke, Mills, Georgieff, & Nelson, 1999; McGrath et al., 2000; Taylor et al., 2000; Taylor, Klein, & Hack, 2000). In a comparison of middle-class ELBW, LBW, and full-term 7-year-olds, Halsey et al. (1996) reported that in contrast to 71% of their LBW and 93% of their full-term sample, only 50% of the ELBW children were in regular classrooms without receipt of special services. Although children in the ELBW group exhibited a high incidence of motor problems, most of their school assistance was language based and designed to improve reading skills. Others have also reported a high prevalence of specific reading and/or math difficulties (Isaacs, Edmonds, Lucas, & Gadian, 2001; Isaacs, Lucas, Chong, Wood, Johnson, Marshall, Vargha–Khadem, & Gadian, 2000; McGrath et al., 2000; Stewart et al., 1999).

Selective deficits in specific domains of cognition, such as memory, attention, language, and executive function, have been explored through the use of standardized or experimental neuropsychological tests. One of the more comprehensive follow-up studies of preterm children has been conducted by researchers in Cleveland, Ohio (Hack, Taylor, Klein, Eiben, Schatsneider, & Mercuri–Minich, 1994; Klebanov et al., 1989; Taylor, Klein, & Hack, 2000; Taylor, Klein, Minich, & Hack, 2000; Taylor, Klein, Schatsneider, & Hack, 1998). Between the ages of 5 and 9 years, preterm
children in this sample scored significantly lower than full-term controls on virtually every measure of cognitive function employed in the protocol, including measures of IQ, adaptive behavior, and school achievement (Hack et al., 1994; Klein et al., 1989; Taylor et al., 1998). Even when analyses were limited to children without neurosensory impairments and with IQ scores in the normal range, VLBW children still performed worse than term controls in overall IQ, basic language skills, perceptual–motor abilities, attention, and planning skills. Deficiencies in verbal learning and nonverbal memory were also evident (Taylor, Klein, Minich, & Hack, 2000). Executive functions were not thoroughly assessed, although these have been the focus of other studies. For instance, Harvey, O’Callaghan, and Mohay (1999) compared ELBW children to age-matched controls at age 4–5 years. Both groups were administered a battery of tasks that included the Peabody Picture Vocabulary Test Revised (PPVT-R; Dunn, 1991), the Tower of Hanoi (Borys, Spitz, & Dorans, 1982), the Finger Sequencing Task (Luria, 1965), and a Tapping Test (Luria, 1973). Parents and teachers completed behavioral questionnaires. Consistent with the findings of de Haan et al. (2000), the premature group performed worse on the PPVT-R, the Tower of Hanoi, the Finger Sequencing task (regardless of which hand was used), and the Tapping Test. The Tower of Hanoi and Finger Sequencing tasks are commonly viewed as measures of frontally mediated executive functions (Luria, 1966; Welsh, Pennington, & Groisser, 1991).

Executive function deficits, particularly in the area of working memory, have also been reported in older school-aged preterm children (Frisk & Whyte, 1994; Luciana et al., 1999). Frisk and White (1994) tested 6-year-olds on a variety of neuropsychological tests. Their sample included three groups of preterm children who varied in whether they had ultrasonographic evidence consistent with no cranial damage, mild lesions, or severe lesions. Cerebral lesions in the preterm children were related to histories of intraventricular hemorrhage. Relative to term-born controls, preterm children with lesions, regardless of severity, were impaired in verbal working memory and sentence comprehension, although the group with severe lesions exhibited a more extensive pattern of impairment. Impairments were observed only on items that were multifaceted. Neither group experienced difficulty on measures of category fluency, learning words in a list, or recalling verbal information after a temporal delay.

Without the use of neuroimaging, it is difficult to make brain–behavior inferences from measures of global intellectual function that are typically used in neonatal follow-up studies. Luciana et al. (1999) attempted to remedy this problem by using a battery of tasks derived from the Cambridge Neuropsychological Test Automated Battery (CANTAB). The CANTAB has been used extensively to measure cognitive dysfunction in brain-injured patients with various etiologies (Fray, Robbins, & Sahakian, 1996). A cohort of premature infants was tested at 7–9 years of age in comparison with age-matched controls. Relative deficits were observed in the preterm sample in pattern recognition memory, memory span (consistent with deHaan et al., 2000), and motor speed, findings that are consistent with damage to periventricular brain regions. In addition, preterm-born children took longer to plan their moves during a modified Tower of London task (Shallice, 1982), made an excessive number of working memory errors on a self-ordered search task, and exhibited poor use of executive strategy in approaching self-ordered search problems. Of 40 preterm children, 18 had reported school difficulties, but significant group differences in cognitive function were still evident when these children were excluded from analysis. When CANTAB scores were correlated with a composite measure of neonatal medical risk, high risk was significantly associated with lower memory span, high spatial working-memory errors, poor use of strategy, and poor performance on difficult items of the Tower of London task. Many of the measures that differentiated the groups are cognitively demanding, require a high level of efficiency, and have been associated with integrity of the PFC in adults (Robbins, 1996). Because the PFC does not attain maximal functional maturity until adoles-
Cognitive development in children born preterm

1033

ence/young adulthood, it is unclear whether the observed deficits represent a developmental lag within the preterm group that will resolve over time or whether these children will experience more profound difficulties on executive tasks as they age.

This question has been addressed by other researchers, using less comprehensive assessment tools. Using a Continuous Performance Test (Loong, 1991), Katz, Dubowitz, Henderson, Jongmans, Kay, Nolte, and deVries (1996) reported relatively poor performance in 6- to 8-year-old premature children with documented neonatal brain lesions as compared to controls. The premature children made more errors of commission and omission, suggesting difficulties with attention and with behavioral regulation. Regression analyses demonstrated that at younger ages, preterm children performed worse than children in the control group. However, performance was equivalent between the groups at older ages.

In an attempt to associate poor cognitive performance at school age with brain volume, Peterson, Vohr, Staib, Cannistraci, Dolberg, Schneider, Katz, Westerveld, Sparrow, Anderson, Duncan, Makuch, Gore, and Ment (2000) measured regional brain volumes in 8-year-old preterm children and matched controls. The WISC-III (Wechsler, 1991) was used to measure IQ, and other neuropsychological tests were administered. The preterm children exhibited significantly lower IQ scores, as well as diminished height, relative to controls. Parent ratings using Achenbach’s Child Behavior Checklist (CBCL: Achenbach et al., 1983) indicated that the preterm children were more likely to be perceived as withdrawn, inattentive, aggressive, and troubled in their thought processes. In addition to these behavioral differences, preterm children exhibited lower regional brain volumes in the cortex, ventricles, basal ganglia, amygdala, hippocampus, and corpus callosum. When total brain volume was entered as a covariate and IVH children were excluded, differences remained significant for the basal ganglia, amygdala, hippocampus, and corpus callosum. The posterior regions of the corpus callosum, which connect sensorimotor regions of the temporal and parietal cortices, were most affected. These areas of regional differentiation were quantified, summed, and then correlated with full-scale IQ scores, yielding a significant association. Low regional brain volume was associated with low full scale IQ. Regional brain volumes were also significantly related to gestational age, 5-min Apgar score, and the presence of an intraventricular hemorrhage. Regional reductions in brain volume have also been reported in the cerebellum of preterm adolescents, and these reductions were also associated with poor scores on global measures of cognition (Allin, Matsumoto, Sant,house, Nosarti, AlAsady, Stewart, Rifkin, & Murray, 2001).

Overall, recent longitudinal assessments suggest a gradient of sequelae with worsening patterns of school-age outcome in the lowest birth weight children and in those who experienced severe intraventricular hemorrhages, PVL, or respiratory distress in the neonatal period (Taylor, Klein, & Hack, 2000). Cognitive outcomes primarily include low scores on global measures of intelligence, although isolated studies have suggested difficulties in almost all measured areas of neuropsychological function, including perceptual–motor skills, visual processing, memory, language functions, and working memory. Some have speculated that the profile exhibited by these children best resembles nonverbal learning disability (McGrath & Sullivan, 2002). Behavioral outcomes include increased prevalence rates of attention-deficit disorder and internalizing tendencies (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Sykes, Hoy, Bill, McClure, Halliday, & Reid, 1997). Academically, preterm children demonstrate lower than expected levels of school achievement and are frequent consumers of special education services (McGrath & Sullivan, 2002; Sia-gal, Houl, Streiner, Stoskopf, & Rosenbaum, 2000). Gender moderates these outcomes, as boys appear to be more disadvantaged than girls. The literature is contradictory regarding whether outcomes change for the worse with increasing age, with some studies reporting higher utilization of special education services and high rates of behavioral problems in older versus younger LBW children (see Taylor et al., 2000, for review). All in all, the literature
paints a rather dismal picture of preterm children’s functioning in the school-age period.

Sociodemographic influences

Notably, sociodemographic and interpersonal variables appear to interact with biological factors to predict individual differences in cognitive functioning (Aylward, 1992). These variables can include distal sources of influence, such as parental education and socioeconomic status, as well as more proximal factors related to family structure, quality of parental care, and other aspects of the home environment. Understandably, mothers of preterm infants report high levels of psychological distress, including depression and anxiety, in the neonatal period as compared to mothers of term-born infants. Regardless of whether their infants are at high or low biological risk, these mothers also report a high level of economic stress. Anxiety levels and fluctuating patterns of depression appear to be prevalent until preterm children reach approximately 3 years of age, at which time mothers of lower risk infants report decreases in economic and psychological distress. However, mothers of infants in both risk groups report high levels of parenting stress, reflecting their perceptions of their children as more demanding, hyperactive, and distractible (Singer, Salvador, Guo, Collin, Lilien, & Baley, 1999). When infants reach 3 years of age, mothers of high risk preterm infants continue to report high levels of family, financial, and personal stress. Singer et al. (1999) also observed significant negative correlations between the severity of maternal depression and their infants’ scores on the Bayley Scales’ Mental Development Index at 8, 12, 24, and 36 months.

To assess whether medical complications or early socioeconomic environment mediated the association between birth status and developmental outcome, Miceli and colleagues (Miceli, Goeke–Morey, Whitman, Kolberg, Miller–Loncar, & White, 2000) tested a preterm neonatal intensive care unit (NICU) sample at 4, 13, and 36 months. Whereas medical complications accounted for outcome at 4 and 13 months, the 36-month outcomes were predicted by the mother’s distress level, as measured by the Beck Depression Inventory (Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961), and her perceived adequacy of social support at 4 months. Maternal distress was positively associated with both internalizing and externalizing behaviors in children at 36 months. Perceived social support was positively related to the child’s linguistic functioning and negatively related to the child’s internalizing behaviors. These findings, although intriguing, are confounded in that maternal distress and child behavior were both rated by the mother. However, using more objective measures and consistent with the findings of other investigators, Landry, Denson, and Swank (1997) reported that whereas medical risk was a significant factor in the determination of 3-year outcome, low socioeconomic status (SES) was independently associated with lags in the development of cognitive and social–communication skills in preterm infants. Similarly, in 5-year-old preterm children, the quality of the child’s home environment was associated with examiner ratings of inattention, impulsivity, and hyperactivity (Robson & Pederson, 1997). Aspects of the child’s home environment that were important included the provision of structured and developmentally appropriate activities to stimulate learning, the presence of a safe and well-organized physical environment, and a social environment that was warm and nurturing.

At school age, both proximal and distal sociodemographic factors may become increasingly salient influences on outcome. Optimal school outcomes at 10 years of age have been associated with increased levels of parental education, rearing by two parents, and long-term stability of family composition and geographical residence (Gross, Mettelman, Dye, & Slagle, 2001). In 6-year-olds with ELBW, Taylor et al. (1998) found that, although neonatal medical risk was the most consistent predictor of behavior, social risk factors independently contributed to the prediction of overall IQ, verbal abilities, and parent-rated behavior problems. Tests of the interactions among risk factors indicated the presence of greater behavioral problems with increasing social disadvantage but only for children at high medical risk. In contrast, oth-
Cognitive development in children born preterm

...ers have reported an opposing pattern where outcomes in high (medical) risk children are largely determined by biological factors, whereas social and environmental influences are more marked for children with less severe medical risk factors (Hack et al., 1992; Koller, Lawson, Rose, Wallace, & McCarton, 1997). The juvenile period in healthy animals is a time during which environmental enrichment influences synaptic architecture in a manner that is beneficial to later behavior (Kolb & Gibb, 2001). Moreover, rats that have experienced cortical lesions during the first week of life and are exposed to motorically and socially demanding environments on a daily basis for a number of months as "behavior therapy" exhibit increases in cortical thickness that are correlated with functional recovery. The provision of tactile stimulation at regular intervals also stimulates recovery. Recall that these are the lesioned animals who exhibit the poorest outcomes and atrophy of cortical neurons in the absence of intervention (Kolb & Gibb, 2001). Given these findings, it is not surprising that environment becomes more important as a determinant of outcome as preterm infants reach school age (although animal studies suggest that behavioral interventions should begin soon after injury in order to foster maximal functional and neural recovery). Given the possibility that these children may catch up to their peers before or during adolescence, intervention strategies directed at individual children's areas of cognitive weakness may be warranted.

Interventions have been attempted during the neonatal and early postnatal period, and these have involved either the provision of increased stimulation to the infant and/or increased social support to families (reviewed in Taylor et al., 2000). Short-term gains are generally evident, but it is unclear whether the gains persist into school age.

Although a number of follow-up studies seem to suggest improvements in abilities from infancy to preschool age, accompanied by declines when the children enter school, findings in adolescent samples are more variable. Longer term studies must be viewed with caution, because many report high attrition rates between infancy and adolescence and few cohorts have reached the young adulthood assessment point. However, a recent report indicates that the majority of preterm children require no special school services by age 14, 75% complete high school, and 40% attend college (Ment, Vohr, Allan, Katz, Schneider, Westerveld, Duncan, & Makuch, 2003). Although encouraging, these gross indicators of functional progress may obscure more subtle aspects of dysfunction that persist or emerge in adolescence.

Adolescence/young adulthood

As has been found in high-risk infants, brain scans of adolescents born preterm continue to show evidence of neural injury. Stewart et al. (1999) examined brain structure and neurocognitive outcome in a cohort of 109 children born in 1979 or 1980 before 33 weeks of gestation. Of the original 109, 72 of these (66%) completed the assessment. These were compared to 21 term controls. Based on neonatal ultrasounds, the brain structure of each preterm infant was described as normal, equivocal, or abnormal. In adolescence, brain structure was again described using MRI. At this time, 56% of the preterm infants had MRI scans that were classified as abnormal, whereas only 5% of control subjects did. Of the abnormal scans, 90% bore evidence of white matter damage. Other consistent abnormalities included ventricular dilation and thinning of the corpus callosum, each of which was associated with a neonatal history of hypoxic–ischemic damage. In terms of continuity over time within the preterm group, 13 cases had been identified at birth with abnormal scans. At ages 14–15, 10 of these were still classified as abnormal, 2 were equivocal, and 1 was normal. Of 59 cases that were identified at birth as either normal or with uncomplicated periventricular hemorrhage, only 16 were normal in adolescence, 13 were equivocal, and 30 were rated abnormal. Preterm birth in general was related to MRI abnormalities, but surprisingly, structural abnormalities bore no clear relationship with neurological outcome, despite the fact that neurological abnormalities were present in 65% of the preterm sample. Reading age was uniformly below expected...
levels in preterm infants regardless of their adolescent classification, although this finding is difficult to interpret because the preterm group was of a lower social class than the control sample. However, a premorbid adjustment score was in the impaired range in those individuals with abnormal or equivocal MRIs. Unfortunately, a comprehensive neuropsychological examination was apparently not conducted, so other structure–function relationships cannot be described.

As in infancy and school age, relative neuropsychological impairments characterize adolescent samples. Of an original cohort of 154 VLBW children, Rickards, Kelly, Doyle, and Callanan (2001) tested 130 (84%) at age 14 years, in comparison to 42 of 60 (70%) control children. Children with major neurosensory impairments, such as cerebral palsy, blindness, and deafness were excluded. A comprehensive neuropsychological battery was administered, parents completed the CBCL, and teachers rated each child’s academic performance. The VLBW children scored significantly lower on the WISC-III’s verbal IQ, performance IQ, and full-scale IQ. Twenty-two children within the preterm group, but only one child in the control group, scored more than 1 standard deviation below the normative mean. Sociodemographic factors moderated the IQ effect to some extent, as IQ scores were higher in children of higher social class, which was scored on a 7-point scale. Every 1-point increase in social class was associated with a 5-point increase in full-scale IQ. However, the group difference in IQ remained significant even when social class was covaried. On the WISC-III, the groups were most different on the Arithmetic and Information subtests. The preterm group also scored lower in math achievement. Bead memory, as measured by the Stanford Binet, 4th Edition (Thorndike, Hagen, & Sattler, 1986), was impaired, and VLBW children obtained significantly lower scores on the Organization Scale of the Rey Osterrieth Complex Figure Task (Lezak, 1995) under direct copy conditions. Teachers reported that more VLBW than control children were in the clinical range on Social Rejection, whereas parents of VLBW children were more likely to rate their children as below average in school. Indeed, VLBW children were more likely to have repeated a grade in school. The VLBW children rated themselves as lower than controls in self-esteem.

These areas of relative impairment that were observed at age 14 were also found previously, when these children were tested at ages 2.5 and 8 years. At age 2.5, they lagged behind their peers on measures of infant development. At age 8, they exhibited significantly lower scores on measures of infant processing, visual memory, and visual perception. Despite this apparent continuity over time, the percentage of concerned parents of VLBW children increased from 20.5% at age 8 to 34.5% at age 14. It may be that as school assignments are becoming more abstract with increasing demands on executive functions, parents are increasingly likely to perceive their children as developmentally delayed.

Curtis, Lindke, Georgieff, and Nelson (2002) compared 32 children aged 11 years with neonatal traumas (NICU) to 25 age- and SES-matched controls. The NICU children nominated friends who served as the control subjects. Twenty-five of the 32 NICU children were preterm children from the sample tested by Luciana et al. (1999) using the CANTAB. Seven of the 32 were full-term infants who were treated in the NICU for severe medical problems at birth. At age 11, the CANTAB was administered as well as the Block Design and Vocabulary subtests of the WISC-III (Wechsler, 1991). Between-group differences were found in spatial memory span and spatial working memory error scores. A composite measure of neurobiological risk was calculated on the basis of a chart review of each NICU child’s neonatal hospital record. Elevated risk scores were associated with lower Block Design scores. Poor spatial memory span was associated with low scores on the WISC-III subtests, as well as low gestational age. Because only 63% of this sample overlapped with the sample studied by Luciana et al. (1999), it is not possible to make direct follow-up comparisons. However, it is worth noting that spatial working memory and spatial span, both of which are mediated by the prefrontal cortex in adulthood (Gold-
Cognitive development in children born preterm

man–Rakic, 1987a; Robbins, 1996), were impaired in preterm children tested at ages 7–9 years in the Luciana et al. (1999) study.

These findings converge with others (de Haan et al., 2000; Frisk & Whyte, 1994; Harvey et al., 1999; Luciana et al., 1999; Ross et al., 1996; Rushe et al., 2001) to suggest the presence of executive function deficits in preterm children over time. However, given that the skills necessary to complete these tasks are still developing in healthy children beyond the age of 11 years (Luciana & Nelson, 2002; Welsh et al., 1991), it may not be possible to make definitive conclusions regarding the integrity of prefrontal functioning until preterm children reach middle to late adolescence. As discussed previously, because executive function deficits are evident when periventricular structures are injured, the presence of these deficits in childhood and their persistence into adulthood argues in favor of striatal damage. In contrast, the sudden emergence of executive function impairment in adolescence or in young adulthood is consistent with early damage to the prefrontal cortex. Prefrontal function might also be indirectly impacted in adulthood by injury to interconnected regions.

The hippocampus and periventricular structures are vulnerable to hypoxia and ischemia (Ben-Ari, 1992), so it is not surprising to find that measures dependent on these structures are compromised. Given the interconnections between the hippocampus and prefrontal cortex, as well as prefrontal–striatal connections, it is logical to expect that cognitive dysfunction may manifest itself early in life by motor and memory deficits, whereas it appears as prefrontal dysfunction later in development, when the PFC has assumed control over higher forms of behavior. A recent study examined the responses of prefrontal pyramidal cells to dopamine stimulation following early ventral hippocampal lesions (O’Donnell, Lewis, Weinberger, & Lipska, 2002). These lesions appear to be benign during the juvenile period but produce behavioral changes as the animals (rats) mature. Prefrontal projection sites exhibited altered electrophysiological responses, demonstrating excessive firing after dopamine stimulation. Normally, these neurons would exhibit a background suppression of firing, leading to increased signal to noise ratios in the presence of salient environmental stimuli. Given dopamine’s integral role as a facilitator of incentive-motivated behavior (Depue & Collins, 1999), these inappropriate cellular responses may impair the individual’s ability to code salient events. Although O’Donnell and colleagues (2002) discuss these findings relative to the neurodevelopmental hypothesis of schizophrenia, they would seem to provide a possible mechanism through which prefrontal function could be altered in preterm children who have sustained periventricular (hippocampal) injury.

Indeed, Isaacs et al. (2000) recently reported diminished hippocampal volumes in preterm children at age 13. These researchers also administered a battery of neuropsychological tests, including measures of IQ, verbal and nonverbal memory, verbal and nonverbal learning, and “everyday” memory, as measured by subtests from the Rivermead Behavioral Inventory (Wilson, Cockburn, & Baddeley, 1991) and by parental responses to a questionnaire. Everyday memory refers to memory for things such as remembering to write down a phone message, keeping track of daily routines, or finding one’s way in a new place. Preterm children differed from age-matched controls on verbal IQ, although both groups scored overall in the average range. In addition, they were particularly deficient on the WISC-III’s Freedom from Distractibility factor, which includes the Arithmetic and Digit Span subtests (Wechsler, 1991). Forward digit span was equivalent between groups, but they differed on backward span. Several differences in memory and learning were also observed, although the authors note that these differences may be due to superior performance in the control group as opposed to deficient performance in the preterm group. A specific deficit in math achievement was also evident. Additionally, the preterm children displayed deficits on several measures of everyday memory, including prospective memory, immediate and delayed route finding, and orientation. Parents also reported differences on a number of items related to these behaviors. In terms of relevant
MRI findings, only 1 of 11 preterm children had a normal scan. Preterm children exhibited bilateral reductions in hippocampal volume, and mean hippocampal volume predicted Rivermead test scores ($r^2 = 0.45$). Some of the measures assessed by the Rivermead inventory, such as prospective memory, could be attributed to prefrontal, as well as hippocampal, function. Because the authors limited their neuroimaging focus to the hippocampus, it is not known whether abnormalities in other areas such as the basal ganglia or PFC might also have been evident.

Consistent with these findings, Maguire, Vargha–Khadem, and Mishkin (2001) describe the case of a 22-year-old man who was born after 26 weeks of gestation. His early course was notable for multiple episodes of hypoxia and ischemia. Although this patient achieved a full-scale IQ in the above average range, he experienced episodic memory difficulties since childhood, specifically in areas of everyday memory, as described above. Structural scans reveal bilateral hippocampal atrophy in addition to possible gray matter loss in the putamen and other periventricular regions. Notably, when asked to perform a memory retrieval task in the context of a functional scan, this patient activated the hippocampus in much the same manner as did control subjects. However, he also activated several brain regions in the frontal cortex that control subjects did not (perhaps suggesting that the task was more effortful for him) and tended to show more areas of bilateral activation, which might reflect plastic changes in the network supporting memory function. Indeed, his hippocampi and medial PFC were more active during the retrieval of events that he consciously remembered versus those that he could not remember in a manner that indicated a distinct pattern of hippocampal–cortical connectivity.

Frontostriatal impairment is further suggested by more subtle indices of executive dysfunction in preterm children during adolescence. Rushe and colleagues (Rushe, Rifkin, Stewart, Townsend, Roth, Wyatt, & Murray, 2001) administered a comprehensive neuropsychological testing battery and reported that preterm children followed at age 14–15 years differed from full-term controls only on a measure of verbal fluency (the FAS test). Scores on this test correctly classified 77% of the preterm children and 70% of control children using a discriminant function analysis, and group differences remained after SES and history of school problems were controlled. The preterm group consisted of 75 children, who comprised 83% of this group’s (Stewart et al., 1997, described above) original sample. A substantial number of these children exhibited white matter abnormalities on MRI, but the MRI abnormalities did not predict poor performance on the verbal fluency test. Because these children had exhibited a number of significant differences in cognition, as compared to control subjects, earlier in childhood, the authors conclude that their findings support evidence of neural plasticity. However, it might also be the case that as the brain is maturing and in the context of a normative functional reorganization, impairment is becoming increasingly focused within the realm of executive behaviors.

In contrast to these findings, Tideman (2000) followed a Swedish sample of preterm infants, examining their cognitive development at ages 4, 9, and 19 years relative to term controls. The original sample consisted of 46 preterm children, 39 of whom completed the 19-year-old follow-up. Cognitive tasks administered included several Wechsler Adult Intelligence Scale subtests (Wechsler, 1997), Raven’s Progressive Matrices (Raven, 1996), the Trail-Making Test (Boll, 1981), and self-report measures of attention at age 19. The Trail-Making Test consists of two parts, A and B, and is utilized in clinical neuropsychological assessment to index frontal lobe function (Lezak, 1995). Trails A requires a person to connect numbered dots in a sequence under timed conditions. Trails B is more complex, requiring alternation between numbers and letters in connecting the dots. When these children were 4 years old, they differed from controls on the Griffith’s Mental Development Scale (Swedish version, Alin–Akerman & Nordbert, 1980), a global measure of intellectual function, but still exhibited scores in the normal range. However, a large number endorsed involvement in
speech therapy. At 9 years of age, there were no significant differences between groups. At age 19, the only test on which the groups differed was Trails B. However, when performance on this task was adjusted for IQ and maternal education, the significant difference disappeared. For the group as a whole, mother’s education was significantly correlated with IQ at age 19 \( (r = 0.43) \). Notably, educational attainment was higher in the term versus preterm children, but both groups were performing at a level commensurate with the Scandinavian norm. Thus, in this admittedly small and relatively healthy preterm sample, cognitive differences observed at age 4 were not evident at ages 9 and 19.

The most comprehensive follow-up of a preterm sample was recently reported by the Cleveland group (Hack et al., 2002) who described cognitive and social functioning in VLBW infants at age 20 years. Preterms were compared to full-term controls who were comparable in SES, although the preterm sample consisted of mothers with significantly lower levels of education. Several differences were evident between groups. The VLBW individuals had higher rates of chronic conditions, primarily neurosensory impairments, as well as shorter overall height. Fewer of them graduated from high school, graduated on time, or were enrolled in postsecondary education. Consistent with these findings, they also scored lower on tests of academic achievement. VLBW individuals also exhibited lower IQs than controls, with an average full-scale IQ of 87.0 versus 92.0 in the control sample. Within the preterm sample, there was also a higher rate of individuals with subnormal or borderline IQs, which has also been reported in studies of younger children (Rose & Feldman, 1996).

However, what was unique about this study is that it also included measures of social and risk-taking behaviors. Relative to full-term controls at age 20, VLBW children reported lower levels of alcohol use, lower frequencies of marijuana use (particularly among women), and (for males) fewer contacts with law enforcement officials. In the control group, males who reported contacts with police indicated that these contacts were related to truancy and substance-use issues. VLBW females reported lower frequencies of sexual activity, pregnancy, or delivering a baby. These differences remained significant when individuals with subnormal IQs or sensory handicaps were excluded from the sample. The authors and commentators (McCormick & Richardson, 2002) interpret this pattern of low risk behavior in the preterm sample as an unexpected relative strength. However, consistent with the findings of Kolb and Whishaw (1981) who reported deficits in species-typical behaviors in rats with early frontal lobe lesions, Hack et al.’s (2002) findings might be interpreted differently. Within the study’s inner city cohort, one might argue that some level of risk-taking behavior represents the social norm. Failure to engage in such activities, at least at the level of experimentation, might reflect developmental delay in areas of potential biological significance, such as sexual behavior.

To summarize, adolescents who were born preterm exhibit indications of early brain injury, such as ventricular dilation, on brain scans. They continue to differ from age-matched controls in their levels of global intellectual function and on selected measures of executive function. However, these differences are sometimes mitigated when sociodemographic factors, such as maternal education, are controlled (Tideman, 2000). Unfortunately, these studies are often plagued by high attrition, small sample sizes, and narrow assessments of discrete cognitive functions.

**Conclusions**

Returning then to the predictions regarding outcome in preterm infants, there is general support for the majority of hypotheses derived from examining controlled studies of animal subjects. The first prediction was that infants born preterm, during the third trimester of pregnancy when neural migration is still in progress, would experience poor cognitive outcomes relative to infants born at term. Regardless of whether comparisons are made in the infancy, preschool, or school-age period, this prediction is supported. Relative to control samples, preterm children exhibit higher
than average rates of mental retardation (Hack et al., 2002; Rose & Feldman, 1996), although this outcome is not the most prevalent. Preterm children generally score lower than term controls on global measures of intellectual function (Rose & Feldman, 1996; Taylor et al., 2000), and they experience relative deficits in language skills (Frisk & Whyte, 1994; Landry et al., 1990; Tideman, 2000; Taylor et al., 2000), explicit memory (deHaan et al., 2000; Isaacs et al., 2000; Taylor et al., 2000), attention (Katz et al., 1996; Robson & Pederson, 1997), and executive functions (Curtis et al., 2002; Frisk & Whyte, 1994; Halsey et al., 1996; Luciana et al., 1999; Rushe et al., 2001). They also experience relative lags in academic achievement (Hack et al., 2002; Halsey et al., 1996). Distinct patterns of social interaction and risk-taking behaviors have also been reported (Hack et al., 2002; Landry et al., 1998). Interpreted from a clinical neuropsychological perspective, the range of difficulties experienced by these children, if they were present simultaneously within a given individual, would suggest the presence of a diffuse pattern of neural damage consistent with damage to white matter tracts that interconnect multiple cortical and subcortical regions. This type of damage provides one of the most difficult diagnostic challenges in neuropsychology for several reasons. First, it is not easily visualized on brain scans, leading to uncertainties about whether there has been actual structural compromise within neural circuits. Thus, individuals with this type of impairment can be mistakenly diagnosed with psychiatric disorders (Lezak, 1995). Second, diffuse patterns of injury can lead to behavioral manifestations that are subjectively meaningful to an individual, usually because they impact the efficiency of information processing, but the level of function (in an absolute sense) is not necessarily in an impaired range. Accordingly, it is important to highlight that across most of the cited literature, the functional differences between preterm children and term-bom controls suggest relative, but not absolute, deficits. Whereas preterm children exhibit lower than expected levels of function, they are still performing within the average range of overall ability, but the level is roughly two-thirds of a standard deviation below comparison groups in overall IQ (Rose & Feldman, 1996; Taylor, Klein, & Hack, 2000). It may be that this general decrement in cognitive performance is due to inefficiencies in information processing, as suggested by some researchers (Rose & Feldman, 1996).

The second prediction was that this behavioral compromise would be paralleled by evidence of brain injury, including diminished brain volume and damage to periventricular, hippocampal, striatal, and frontal lobe structures. Although findings are not consistent across studies, neuroimaging of preterm infants in early infancy suggests a high prevalence of white matter damage (Huppi et al., 1996; Maalouf et al., 1999). Diminished total brain volume has been reported in at least one study of school-age children (Peterson et al., 2000), and regional variations in structure predict low levels of cognitive function (Allin et al., 2001; Isaacs et al., 2000; Peterson et al., 2000). Consistent with the neural evidence of white matter damage, preterm infants consistently exhibit difficulties on visuomotor tasks during childhood. At least one cohort has been scanned during adolescence (Stewart et al., 1999), and evidence of structural brain injury (ventricular dilation, white matter abnormality) is evident. The findings are inconclusive regarding whether the PFC is specifically damaged or whether its functioning is compromised because of damage to the pathways connecting it to the striatum and hippocampus.

The third prediction was that evidence of substantial neural damage observed in the neonatal period would remain stable over time, suggesting limits to the brain’s ability to compensate for severe injury. Although many studies report changes in children’s classifications as “normal,” “abnormal,” or “suspect” as development proceeds (Fazzi et al., 1999; McGrath et al., 2000), a consistent finding is that children who are identified early as having major sequelae of preterm birth (leading to an early classification of abnormal) remain so as they mature (Dewey et al., 2000; Fazzi

However, it was also predicted that in children with more subtle indications of neural abnormality, outcome must be considered from a lifespan perspective, because recovery may not be evident until adulthood or sleeper effects will emerge at that time. Conclusions are speculative regarding this prediction, because very few studies have followed children through adolescence and into young adulthood. Isolated longitudinal studies of young adults who were born preterm (Stewart et al., 1999; Tideman, 2000) suggest recovery of function, although the samples across these studies are not equivalent with respect to degrees of prematurity, birth weight, and SES. In addition, no studies of adolescents or young adults who were preterm employed comprehensive neuropsychological testing including rigorous measures of executive function. Instead, relatively simple tasks, such as the Trail-Making Test and the Verbal Fluency task (each of which takes about 5 min to administer) have been implemented (Rushe et al., 2001; Stewart et al., 1999; Tideman, 2000). Although poor performance on these tasks is undoubtedly meaningful, adequate performance in a laboratory setting is more difficult to interpret. Given that deficits in executive and organizational skills typically emerge under conditions of high stress where structure must be self-imposed (Lezak, 1995), this area of assessment could be considerably improved, perhaps by including measures that require multi-tasking or strategic thinking (Luciana et al., 1999).

A host of factors (summarized in Figure 2), including genetic, sociodemographic, and congenital variables, determine the nature of cognitive development in the preterm-born child. As emphasized in this review, congenital factors have been extensively researched and it is clear that preterm children who are most ill during infancy are at high risk for later impairments. Given the high prevalence of preterm birth among women of low SES, many researchers have also attempted to relate children’s cognitive dysfunction to demographic variables. Relatively high SES and a warm but stimulating home environment appear to act as protective factors. Indeed, this finding was anticipated a number of years ago. In their now-classic paper regarding the interaction among biological and sociodemographic factors in determining outcome following early adversity, Sameroff and Chandler (1975) stated that “transactions between the child and caretaking environment serve to break or maintain the linkage between earlier trauma and later disorder and must . . . be taken into account if successful predictions are to be made” (p. 190). The literature on preterm birth is sorely limited by samples that lack sufficient heterogeneity to test this model. For example, of the studies reviewed in this paper, most included control samples of children matched on various demographic factors, such as maternal age, education, and family income (Curtis et al., 2002; de Haan et al., 2000; Dewey et al., 2000; Gross et al., 2001; Hack et al., 2002; McGrath & Sullivan, 2002; Peterson et al., 2000). However, many of these samples fail to span the full range of socioeconomic diversity (for example, Halsey et al., 1996; de Haan et al., 2000; Hack et al., 2002; Koller et al., 1997; McGrath et al., 2000; Rose & Feldman, 1996), and many researchers fail to consider socioeconomic characteristics in their analyses (Fazzi et al., 1997; Huppi et al., 1996; Isaacs et al., 2000; Katz et al., 1996; Luciana et al., 1999; Maalouf et al., 1999). More proximal sources of influence are also important but rarely studied. For instance, interactions among parents’ affective states, the child’s temperament, and the quality of infant–mother attachment may be important moderators of outcome in infancy (Blair, 2002; Poehlman & Fiesse, 2001).

Arguably, our ability to structure helpful interventions in individual cases partially relies on the ability to predict what the child’s level of function might have been in the absence of preterm birth. This type of prediction would presumably rely on knowledge related to sociodemographic and emotional features of the child’s immediate environment as well as genetic influences. None of the studies reviewed here incorporated genetics into their
models by describing, for instance, the relationship between a child’s cognitive status and that of his or her parents or term-born siblings. Neural plasticity is not without limits (Kolb, 1995), and those limits will partially depend upon the child’s intellectual temperament in conjunction with the timing and nature of injury. Another difficulty that characterizes this area of research is that small sample sizes limit the extent to which interactions among risk variables can be statistically inferred.

To conclude, preterm birth is a relatively common but unfortunate event that confers many stresses, physiological and experiential, upon the child and his or her family. In the midst of a number of personal challenges that affected families must face, prospective studies of premature infants have the potential to revolutionize developmental theories of plasticity by permitting the examination of interactions among biological risks and individual experiences. This population of infants provides developmental neuroscientists and psychopathologists with a unique opportunity to observe the extent to which the developing brain can recover from early brain injury or, in the case of healthy preterm infants, from earlier than expected exposure to the extrauterine world. As highlighted in this review, although animal studies provides a context that can productively guide these observations, controlled manipulations cannot approximate the complexity of human development. At times, this complexity is daunting, as suggested by the title of a recent commentary (see Aylward, 2003).

In experiments conducted under controlled conditions, participants are ideally representative of a given population and randomly assigned to treatment and control conditions. Natural experiments are those in which this assignment occurs spontaneously. In the case of preterm birth, the time of birth is the independent variable of interest, and preterm-born children are compared to term-born peers. Brain imaging at birth and again at the expected due date can be utilized to ascertain how the structure of the nervous system changes in the time period that typically characterizes late gestation (e.g., 6–9 months postconceptional age). These structural changes can be correlated with indices of behavioral progress. Thus, preterm-born children inform developmental theory, because they provide researchers with a unique temporal window through which to observe the dynamics of early brain maturation. Because even healthy preterm infants lag term-born controls in their early development, these observations primarily serve to enhance our understanding of how early experience shapes later behavior. In addition, they challenge the assumption that development occurs similarly outside of the womb.
as it would have occurred prenatally. As discussed in this review, preterm infants are psychologically unprepared for the postnatal environment within which they must suddenly function. Meeting these environmental demands comes at some (often considerable) cost, and earlier than expected stimulation may be impinging upon a neural system that cannot benefit from it. Despite these many ways in which studies of preterm infants have informed developmental theory, such experiments of nature are, by definition, fraught with variables that are beyond scientific control. These variables largely relate to individual, family, and sociocultural influences that have been recognized as important but which have not been adequately investigated. Characterization of these experiential variables and how they interact with biological factors is the next great hurdle to be negotiated in this research arena.

Another hurdle is to recognize that a description of relative deficits is insufficient to account for the quality of life experienced by preterm infants as they mature. How these deficits are reflected in real-world competencies (Waters & Sroufe, 1983) must be investigated in order to develop models regarding dynamic relations among brain injury, discrete measures of outcome, and lifespan success. Despite a number of unavoidable limitations, this goal is unlikely to be attained without improvements in research methodology. The longitudinal assessment of preterm infants could be significantly improved through (a) the initiation of multicenter investigations that would permit larger numbers of infants to be assessed and multivariate models of risk to be evaluated, (b) the inclusion of an array of brain-based neurocognitive assessments applied to children and to their parents or siblings across their life spans, (c) assessment of proximal sources of influence on early development, and (d) adoption of a sufficiently prospective approach in recognition of findings indicating that, although progress can be inferred through discrete assessments, functional outcome is illusory and must be considered from a life-span perspective.

References


mental Psychopathology, Vol. 4, Developmental per-


Dammann, O., Kaban, K. C., & Leviton, A. (2002). Peri-

Dammann, O., & Leviton, A. (1997). Maternal intrapar- 
tine infection, cytokines, and brain damage in the pre-


cvice.


rics, 70, 670–676.

Fazzi, E., Orcesi, S., Telesca, C., Onetto, A., Rondini, G., & Lanzi, G. (1997). Neuromotor, perceptual and fine motor outcomes in very low birth weight infants at 24 months, and 5 to 7 year of age: Changing diagnosis. Pediatric Neuro-

rology, 17, 240–248.

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuropsychiatric applications of CANTAB. Interna-


Frisk, V., & Whyte, H. (1994). The long-term conse-

quences of periventricular brain damage on language and verbal memory. Developmental Neuropsychology, 10, 313–333.

Fuller, P. W., Guthrie, R. D., & Ellsworth, D. A., Jr. (1983). A proposed neuropathological basis for learn-
ing disabilities in children born prematurely. Develop-


Goldman, P. S. (1971). Functional development of the prefrontal cortex in early life and the problem of neu-


bectomy in infant monkeys. Experimental Neurology, 29, 221–226.

Goldman–Rakic, P. S. (1987a). Circuity of primate pre-

frontal cortex and the regulation of behavior by repre-


ment of the prefrontal cortex: Evolution, neurobiol-

ogy, and behavior (pp. 27–48). Baltimore: Brooks.


Hack, M., & Fanaroff, A. A. (1999). Outcomes of chil-


Hack, M., Flannery, D. J., Schluchter, M., Cartar, L., Borawska, E., & Klein, N. (2002). Outcomes in young adulthood for very low birth weight infants. New En-

gland Journal of Medicine, 346, 149–167.

Cognitive development in children born preterm


Cognitive development in children born preterm


