J Perinat Neonat Nurs
Vol. 24, No. 4, pp. 356–365

A Model of Neurodevelopmental Risk and Protection for Preterm Infants

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The purpose of this article is to introduce a model of neurodevelopmental risk and protection that may explain some of the relationships among biobehavioral risks, environmental risks, and caregiving behaviors that potentially contribute to neurobehavioral and cognitive outcomes. Infants born before 30 weeks of gestation have the poorest developmental prognosis of all infants. These infants have lengthy hospitalization periods in the neonatal intensive care unit (NICU,) an environment that is not always supportive of brain development and long-term developmental needs. The model supports the premise that interventions focused on neuroprotection during the neonatal period have the potential to positively affect long-term developmental outcomes for vulnerable very preterm infants. Finding ways to better understand the complex relationships among NICU-based interventions and long-term outcomes are important to guiding caregiving practices in the NICU. **Key words:** *cognitive development*, *feeding patterns*, *neurobehavior*, *neuroplasticity*, *preterm infant*

Although the survival rate of very preterm infants exceeds 85%,[1] neurobehavioral disabilities including cerebral palsy and severe neurosensory impairment occur in 5% to 15% of the survivors.[2] Moreover, an estimated 50% to 70% of very low-birth-weight preterm infants (≤1500 g) have later dysfunction, including cognitive, behavioral, and social delays that impede school progress.[3] These difficulties often persist into adulthood,[4] making preterm birth one of the most costly and devastating of all health events with nearly $18 billion spent yearly on the initial hospitalization alone and untold additional costs related to adverse neurobehavioral and cognitive outcomes.[5]

Developmental outcomes of children born preterm are heterogeneous, yet the risk of poor neurobehavioral outcomes is high.[6–10] A major reason for increased risk is the structural differentiation (ie, neuronal differentiation, glial cell growth, myelination, axonal and dendritic growth, and synapse formation) of the central nervous system that occurs rapidly between 23 and 32 weeks of gestation and the possibility of alterations in differentiation that may affect later development.[11] Outcomes in preterm infants are additionally mediated by environmental experience, such as the noxious nature of the neonatal intensive care unit (NICU),[12,13] including handling of preterm infants by multiple caregivers. Even when efforts are made to improve caregiving with developmental care models,[14–16] the incidence of poor neurobehavioral outcomes is high, perhaps because of the complex relationships among

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This work was supported in part by grants R01 NR00512 (R.H.P, PI), R15 NR09235 (J.M.M., PI), and P20 NR008988 (N.M., PI).

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Submitted for publication: June 28, 2010
Accepted for publication: September 6, 2010

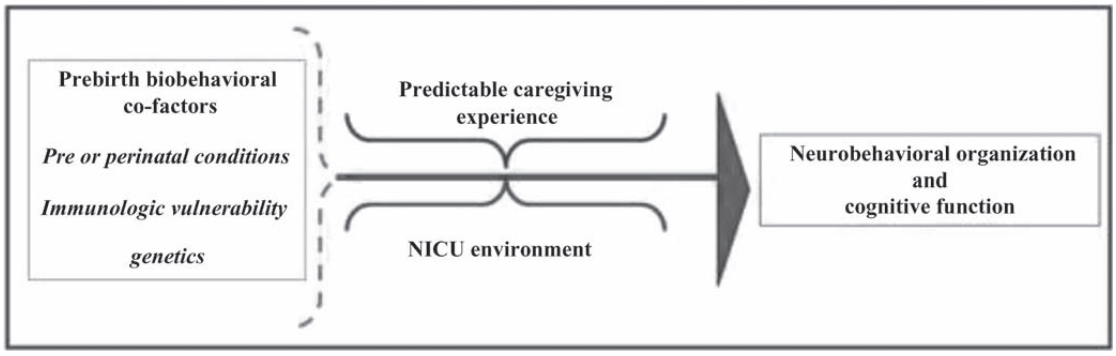

Figure 1. A model of neurodevelopmental risk and protection.

biobehavioral and environmental risks, caregiving behaviors, the timing, size, and site of brain insults, and the timing and type of interventions.[17]

This article introduces a model of neurodevelopmental risk and protection that may explain some of these relationships (Figure 1). As the model illustrates, a number of factors contribute to poor cognitive function (CF) and neurobehavioral organization in children who are born preterm. In addition, the risks of poor outcomes may be influenced by the experiences of the infant, including those associated with the NICU and caregiving interventions. We begin by outlining what is currently known about preterm infant brain development and factors that may affect brain development. From there we outline a simple framework to implement neuroprotective intervention of patterned feeding that has the potential to positively affect developmental outcomes for these at-risk infants.

THE PRETERM INFANT BRAIN

The human brain has more than 100 billion neurons that are connected into networks and systems that mediate specific functions according to primary neurotransmitter networks, synaptic structure, and regional localization (see table 1 for definitions). All systems, however, have similar rules mediating development, response to chemical signals, and storage of information from the external (visual, tactile, olfactory, and auditory) and internal (hormonal signals associated with hunger) environments.[18] Neuronal systems enable a child's cognitive development, including executive function (EF), that is necessary for higher-level thinking and learning. The development of neural networks depends on both molecular cues that guide synapse development and activity-dependent mechanisms that use patterned activation to adjust the strength and number of synaptic connections.

Executive function emerges in infancy and continues to develop throughout childhood.[19] Executive function encompasses goal-directed behavior that is deliberate, conscious, and purposeful. While dependent upon basic cognitive processes such as perception and memory, EF is associated with higher-order cognitive abilities, including working memory, inhibitions, and planning. It is generally agreed that EF is primarily governed by the prefrontal cortex of the brain and the emergence of EF abilities coincides with the development of this area of the brain. However, the prefrontal cortex is late to mature in fetal development, with continuing development during infancy. Thus, it may be particularly vulnerable to damage in preterm newborn infants; EF deficits are associated with preterm birth and related medical complications as well as the noxious environment and caregiving in the NICU.[20,21] Executive function deficits are linked to a range of problems, including attention-deficit disorder, learning difficulties, and autism, all of which are more prevalent in children born preterm.[22]

Neural plasticity

The brains of infants are noted for plasticity, especially during and after neuronal migration when synaptic formation (ie, synaptogenesis) is occurring, a process that may continue throughout life but that largely occurs during fetal, infant, and early childhood development.[23] Molecular changes permit the storage of information by neurons and neural systems, allowing the brain to be responsive to the environment. The more frequently a neural connection (synapse) is stimulated, the more likely it is to become permanent.[24]

Table 1. Glossary of terms related to brain development

1) ***Synapse***: electrical connections between 2 or more neurons that support communication between the neurons
a. ***Neural transmitter***: supports synaptic connections, usually enzymes, act to excite or inhibit the activity of the next neuron
b. ***Synaptogenesis***: process of how neuronal connections are made; initially are genetically initiated
c. Synaptic or neural networks: support and direct human behavior, number in the trillions in adulthood, activated in response to both internal cues (ie, critical periods in development or hunger) and external cues in the environment (ie, light, noise, activity changes)
d. ***White matter***: groups of interconnected myelinated neurons through axons (via neuronal connections) connect various gray matter areas of the brain to each other
e. Grey matter: more highly populated with neural cell bodies, in contrast to white matter
2) **Apoptosis**: programmed cell death that occurs when cells are no longer needed or used
3) **Glial cells**: nonneural cells in the brain that physically support, provide nutrition, and protect all the activities of the neurons
a. ***Astrocytes***: a type of glial cell that mainly supports and feed the neurons and their connections
b. ***Microglia***: a type of glial cell act as immune defense for the central nervous system

Thus, the more a neural network is stimulated, the more there will be internalization of new information; neural activations that are not reinforced with experience are lost. Thus, experience creates a template through which new input is filtered. However, plasticity can be adaptive or maladaptive, depending on the experience and the brain's response. Moreover, changes can occur at multiple levels, including physiological (ie, the release of more neurotransmitters to compensate for cell death), anatomic (ie, the extension of existing axons into space vacated by deleted axons), and metabolic (ie, the brain's ability to grow capillaries in an area to suit a new function such as occurs with learning).

The human brain is functionally altered through experience, and all experience is filtered by the senses (touch, taste, smell, sound, and sight). These sensory signals initiate a cascade of cellular and molecular processes in the brain that alter neuronal neurochemistry and, ultimately, brain structure. Two mechanisms to explain how synapses are formed on the basis of experience have been proposed, experience-expectant, and experience-dependent.[25] Experience-expectant development is a process in which synapses form after some minimal experience is obtained. These unpatterned, temporary synapses are dispersed within a relatively wide area of the brain during sensitive periods, providing a structural substrate of expectations. These synapses require repeated stimulation in the form of neural activity for survival; the expected experience produces patterns of neural activity. If synapses do not form connections or form abnormal connections, they do not survive. In contrast, experience-dependent development is that in which synapses develop in response to unique aspects of the environment such as occurs with learning. The most appropriate experiences for the preterm infant's neurologic system are those that take advantage of both types of synaptic development.

NEUROBEHAVIORAL ORGANIZATION AND COGNITIVE OUTCOMES IN INFANTS BORN PRETERM

Neurobehavioral organization, the use of goal-directed states of consciousness in interaction with the caregiving environment,[26] is observed in the infant's biobehavioral repertoire, including neurologic integrity, learning, perception, and social interaction.[27] Preterm birth is associated with high rates of both poor neurobehavioral organization and CF.[28]

Preterm infants may suffer early neurologic injury caused by intraventricular hemorrhage or white matter damage leading to periventricular leukomalacia , or the death of brain tissue.[29] There is also evidence that even preterm infants without these injuries may develop cognitive dysfunction,[30] with diminished levels of attention, memory, and reasoning skills.[31] Lower IQ scores and CF have been noted in children and young adults born preterm,[32] and these were significantly correlated with prematurity.[33] Even without severe intraventricular hemorrhage (grades III or IV), CF, and visual motor abilities are substantially impaired and there is a higher incidence of attention-deficit/hyperactivity disorder when compared to term-born controls.[34] Decreased CF in children born preterm is associated with a higher incidence of motor and mental impairments and with significantly lower educational achievements, even after adjusting for sociodemographic status.

Perinatal risk factors (eg, hypoxia, hemorrhage, severity of illness) or demographic factors (eg, gender, minority status, maternal education) do not explain these outcomes, pointing to subtler and more pervasive influences on brain development. Increased

neuronal death in the immature brain may offer 1 explanation because immature neurons are very vulnerable to degenerative changes and apoptosis, the process of programmed cell death that may become excessive in the presence of ischemia. While many adverse neurodevelopmental outcomes are observable in early infancy, the effects of neurologic dysfunction become more obvious only with increasing age. These dysfunctions, including learning disorders, attention-deficit/hyperactivity disorder, and behavioral problems, occur in as many as 50% to 70% of children born preterm and are likely affected by a combination of genetic factors, prenatal or perinatal injury, and a mismatch of extrauterine environment to organism need.

POTENTIAL COFACTORS FOR NEUROBEHAVIORAL AND COGNITIVE OUTCOMES

Many factors contribute to poor neurodevelopmental and cognitive outcomes in preterm infants. These factors can generally be categorized into prebirth biobehavioral cofactors (prenatal or perinatal events or conditions, immunologic vulnerability, genetics), the mediation of the NICU environment (light, sound, caregiving experiences), and moderation by family and postdischarge caregiving. For this article, we focus on factors that are in place prebirth and those associated with mediation from the NICU environment. It has been hypothesized that persons exposed to an adverse fetal or neonatal environment develop compensatory physiological responses to survive and that these responses become permanent.[35] These changes may be maladaptive over time if they result in changes to normally expected systems of functioning. Thus, there is evidence that early experiences, both good and bad and both biologic and behavioral, influence both short- and long-term outcomes in children born preterm.

Prebirth biobehavioral cofactors

Some of the factors implicated in poor neurobehavioral or cognitive outcomes in preterm infants include hypoxic/ischemic insults, maternal infection with overproduction of cytokines, and other proinflammatory agents, excessive glutamate release initiating the excitotoxic cascade, oxidative stress, growth factor deficiency, specific maternal drugs, and maternal stress.[36] White matter cells are the precursors of myelinating oligodendrocytes, which constitute a major glial or nonneuronal population in the white matter; these cells are highly vulnerable to oxidative stress[37] such as may occur in response to repeated insults including inflammation. White matter damage occurs where there is exposure to proinflammatory cytokines (ie, interleukin [IL]-1β, IL-6, or tumor necrosis factor [TNF-α]), a situation that potentiates abnormal cortical development.[38] Among noxious factors present in utero, some may be sufficient to cause permanent injury to the developing brain before birth whereas others may act as predisposing factors that increase susceptibility to later injury. Understanding this process is crucial to the development of effective strategies that protect the developing brain (ie, neuroprotective strategies).[39]

Prenatal and perinatal events and conditions

Prolonged time between membrane rupture and delivery and multiple placental lesions may affect neurobehavioral organization and later CF in preterm infants.[40] Other associations include pharmacologic treatment during pregnancy with steroids and other medications, primiparity, and maternal diseases such as pregnancy-induced hypertension, diabetes mellitus, or chorioamnionitis,[41] as well as perinatal or birth asphyxia and intrauterine growth restriction .[42] Low Apgar scores, neonatal acidosis, elevated C-reactive protein, septicemia, and anatomic abnormalities of the brain may also complicate outcomes.[43] Prenatal and postnatal infections are also potentially harmful to the developing brain, and fetal exposure to inflammatory cytokines may reduce the threshold at which hypoxia becomes neurotoxic, making the brain much more vulnerable to even mild hypoxia such as occurs during labor.[44]

An important aspect of cytokine biology is the high degree of overlap in source, target cell, and function, making it difficult to identify individual cytokines as "most important." In addition, some cytokines have opposing (pleotropic) functions (eg, IL-6 is both a pro- and anti-inflammatory cytokine). Moreover, fetal and neonatal inflammatory responses occur at multiple levels. At the brain level, the neuroinflammatory response is of crucial importance. The timing of insults during brain development is also an important factor and may explain some of the differences in outcomes between term and preterm infants who experience similar insults.[19]

In utero exposure to inflammatory processes greatly increases the risk for long-term negative outcomes,[45–47] possibly because of resulting placental insufficiency. Both placental insufficiency and exposure of the fetus to proinflammatory cytokines may lead to white matter damage,[48,49] which is associated with increased levels of the cytokines IFN-γ, IL-6, and IL-8 up to 72 hours

after birth.[50,51] White matter damage is most closely associated with immaturity and the fragility of tissues in the brain that make them susceptible to hemorrhage and periventricular leukomalacia.[52] In addition, elevated neonatal proinflammatory cytokines, also known as chemokines, suggest an important role of inflammation following brain injury early on (IL-1β, TNF-α, and IL-6)[53,54] and many days later (IL-18, TNF-α, and IFN-γ).[55,56] IL-8, also known as CXCL8, has been particularly implicated in inflammatory processes associated with preterm birth.[57,58]

Genetic cofactors

There is increasing evidence that genetic variation also influences the risk for brain damage related to inflammation. Some of the most intriguing data come from studies of genetic variations in apolipoprotein E (ApoE), a lipid transport protein that also plays a role in repair after cell injury.[59] ApoE, produced by glial cells (astrocytes and microglia), has a role in transporting lipids to injured neurons by regulating cholesterol and fatty acid metabolism. In addition, ApoE may mediate synaptogenesis during neurodevelopment. The 3 common alleles of this protein differ only on the basis of 1 or 2 amino acids. Although generally the $\varepsilon 2$ allele is considered normal, early cognitive functioning at 2 years of age is reportedly worse among infants with either the $\varepsilon 2$ or $\varepsilon 3$ allele.[60] In addition, infants with the $\varepsilon 4$ isoform of ApoE, which is generally associated with a greater incidence of Alzheimer's disease, may have advantages over those with the $\varepsilon 2$ or $\varepsilon 3$ isoforms with respect to early-life neuronal and brain development.[61] The explanation of findings associated with these genetic factors remains unknown. Other potential genetic markers of neurobehavioral disorganization or cognitive dysfunction include genes that influence neurotransmitters, such as dopamine, which modulates memory, attention, and frontal-executive functions.[62–64]

NICU environment and caregiving experience

Although the resources of the NICU may save lives, the type of stimulation experienced in this environment is not necessarily compatible with the preterm infant's neurodevelopmental needs. Rather, the typical NICU environment is inherently stressful for infants and their families.[65,66] This mismatch produces maladaptive physiological processes and predisposes the infant to later disease and poorer developmental outcomes.[67–69] Because the NICU environment is unlikely to be conducive to the developing brain, prebirth risk factors may be potentiated, further adversely affecting neurocognitive development. As noted, it has been hypothesized that experience has a profound effect on the cultivation and continuation of synapses; that is, the development of these synapses is activity dependent. Those that are used proliferate, while those that are not used die. In the normal intrauterine environment, this process of synaptic connections works to support the infant's normal development; in the environment of the NICU the opposite may actually be true because the negative experiences of the infant lead to different, abnormal synaptic connections with potentially more deleterious long-term effects.[19] So although there is little research about the effect of caregiving on later CF, there is increasing evidence that early experiences affect brain development and function in infants born preterm.[16] Moreover, the match between environmental experience and neurologic expectation during critical periods of development has been shown to be important,[70,71] and there is little doubt that the NICU environment or our general approaches to caregiving are a good match for the preterm infant's neurodevelopment.

POTENTIAL NEUROPROTECTIVE FACTORS

Neuroprotection encompasses all interventions that promote normal development or prevent disabilities,[72] by acting on the biologic processes involved in cell death. Possible interventions may include proinflammatory cytokine antagonists or glutamate receptor antagonists, or antiapoptotic agents, as well as environmental and caregiving interventions. A major challenge faced by the use of neuroprotective agents or activities in preterm infants is the large number of risk factors and the complexity of mechanisms responsible for development of brain lesions.[73] In addition, the timing of initiation and the actual course of the cascade that leads to brain injuries is not fully understood and there is poor specificity for both fetal stress markers at initiation of the cascade and signs of adaptation. In addition, many agents that protect the brain could also impair plasticity or kill neurons if applied in excessive amounts.[74] Thus, increasing awareness of the role of the environment has led to prevention programs that focus on development such as support of the mother-infant relationship, along with stress-reducing therapies and individually tailored development-enhanced care.[75]

Neuroprotective interventions

Identifying when and how damage occurs is a problem in developing interventions that have the potential to make the most difference. However, animal models have identified that neuroprotective strategies can stop

brain lesions from progressing. Thus, while prevention and early treatment of brain lesions are the most desirable goals for intervention, promoting postlesion plasticity is the attainable target in many cases, given the absence of early markers for brain damage.

For example, much research has focused on "early intervention," programs designed to enhance brain development in infants and young children.[76] Early intervention strategies seek to take advantage of neural plasticity, which is most sensitive 2 to 3 months through 15 to 18 months after term age, congruent with a goal of neuroprotection. A recent review of the effect of early intervention programs revealed that interventions provided prior to 40 weeks postmenstrual age were most effective in promoting cognitive development, regardless of the type of intervention.[77] In 7 studies that evaluated the effect of interventions begun in the NICU with cognitive outcome evaluated by the Bayley Scales of Infant Development or the Griffiths Developmental Scales, 5 reported a beneficial effect of the intervention on cognitive development. These included (NIDCAP) newborn individualized developmental care and assessment program (NIDCAP), auditory-tactile-visual-vestibular intervention, and skin-to-skin holding (kangaroo care). While most intervention programs are aimed at facilitating motor organization, theoretically, stimulation of motor development at critical periods in infancy affects later CF. This is because during early critical periods, the neurologic system explores all possibilities for neural connections and because during this time much variation is possible. Later, the neurologic system is more selective, choosing pathways that already exist to affect action. When there are limited pathways because of poor synaptic development, there are limited choices for ongoing later development.

Individualized developmental care for the infant and family is the primary focus of NIDCAP. Infants and families are assessed regularly and the infants' behavioral cues and responses are used as the foundation for all caregiving. Short-term outcomes including decreased number of days on mechanical ventilation, decreased number of days to full feedings, and shorter length of stays in the NICU have been good. However, long-term outcomes have not been promising and it appears once discharged other environmental and social factors have an equal or greater impact on developmental outcomes.[78,79] Auditory-tactile-visual-vestibular intervention is a multisensory intervention that has shown promise by providing modulated kinesthetic and sensory stimulation to preterm infants greater than 30 weeks postmenstrual age. Short-term infant outcomes, including increased physiologic regulation, have been reported.[80,81] However, there are few studies of long-term outcomes and little data on very preterm infants or infants with known brain lesions. Skin-to-skin holding has also been used with some success as an intervention to increase attachment and bonding while ameliorating many of the negative aspects of neonatal intensive care such as decreasing behavioral responses to painful procedures.[82]

All of these interventions require resources such as expensive training, increased numbers and type of staff, or equipment to enhance the environment, making them difficult to implement for a long term in the NICU environment. To date, despite reported findings, none of these intervention strategies have been integrated into routine caregiving. While skin-to-skin holding requires the fewest resources, it has been difficult to achieve widespread implementation in NICUs because of staff attitudes and beliefs about the time and resources needed as well as the real necessary space and equipment (lounge chairs or recliners) to support the mothers/fathers and their infants.

One way to provide neuroprotective intervention without the need for additional resource allocation is the implementation of interventions that can be easily integrated into routine aspects of care such as feeding. Success at oral feeding is essential to survival. It is also an undertaking shared by the caregiver with the infant such that how the feeding is done can have as much of an overall effect as the nutritional value of the breast milk or formula ingested.[83]

Predictable caregiving experience

Experience during the critical periods of early childhood organizes the connectivity within the developing brain and encourages neurologic maturation.[84] As noted, the more frequently a particular pattern of neural activation occurs, the more permanent the neural connection becomes. In the developing brain, undifferentiated neural systems are critically dependent on environmental cues to activate and support the maturation of neural connections. Lack or disruption of these cues can result in abnormal neural development. Thus, the environment of preterm infants is critical to their long-term development, continuous noxious or inappropriate experiences in the NICU have the potential to change the development of the neurologic system in ways that may not be malleable to future change.

Whether and to what extent plasticity can compensate for failure to develop specific functions at normally expected periods is unknown. The crucial importance of developmentally appropriate caregiving is supported by data about neuronal death, synaptogenesis, and other processes of neurologic development,

all of which depend on experience. Delayed or dysfunctional plasticity with developmentally inappropriate caregiving may be associated with cognitive deficiencies. Thus, providing interventions that decrease inappropriate stimulation has the potential to support more normal development.

Unlike the full-term newborn who provides behavioral cues to caregivers that provoke responsiveness and synchrony within the caregiver-infant dyad, the preterm infant does not offer such cues. In addition, the preterm infant's environment in the NICU is not as predictable in providing the appropriate stimulation to support and enhance neuronal development: caregivers change regularly; medical procedures dictate touch and handling; and little care is based on infant cues. Research supports the positive effects of caregiving that is provided in a predictable framework. Research shows that preterm infants who received care based on their neurobehavioral capabilities are more organized in both motor and autonomic regulation, had better self-regulation, and are more able to calm themselves.[16] In addition, these changes are shown to be persistent to at 9 months of age, resulting in increased motor system organization and enhanced expression of attention and significantly better Bailey motor scores at 12 months of corrected age.[85] However, these positive findings are clouded by the lack of predictability to the interventions, and thus, with their potential to gain widespread use. What may be useful is an approach to caregiving that is timed to occur with a naturally occurring body sensation (ie, hunger), that is provided in a manner that is congruent with the expectation of the neurologic system related to the activity (ie, being held) and that occurs with enough regularity that neuronal and synaptic development is supported. For example, a patterned feeding experience may serve as a neuroprotective intervention to enhance brain development for preterm infants in the NICU if delivered in a developmentally supportive and predictable manner.

Patterned feeding experience: A potential neuroprotective intervention

The contribution of feeding as a skilled nursing or parent intervention has received little research attention. The contribution of the feeding experience to normal development has rarely been examined.[86–88] However, there is evidence that without the opportunity for nutritive sucking during early infancy, the skills needed to perform this task effortlessly may never be perfected.[89] For the preterm newborn, sucking skills develop early and mature over time, with most demonstrating effective regulation of suck, swallow, and breathe by 36 weeks post-menstrual age. This experience coupled with maturation is necessary for development not only of oral feeding skills but also for the achievement of other developmental milestones.[90–92] Research on a predictable oral feeding experience suggests that such a patterned experience might be beneficial to the preterm infant's neurobehavioral development and later CF.[93]

Neuroprotective interventions that enhance the development of a more normal experience for the infant may result in improved neuronal connections and enhanced synaptic development supporting enhanced neurobehavioral organization. This type of intervention takes advantage of neuronal synaptic development and both experience-expectant and experience-dependent characteristics of the developing brain. In addition, the intervention takes advantage of a regularly occurring caregiving and life-sustaining event for an infant, feeding. Regardless of how ill or preterm a newborn is, enteral feeding, by gavage tube early on and later by oral feeding, is an ongoing caregiving activity in neonatal intensive care, one that is usually performed by nurses.

Despite much research on nutritional aspects of feeding as well as strategies to promote oral feeding readiness and feeding progression, much of preterm infants' feeding experience remains a trial-and-error activity. There are no widely accepted protocols for initiation or progression of enteral feedings, and even fewer accepted protocols for initiation of the oral phase of those feedings. Even recent reports of "cue-based" oral feeding initiation and progression are not built on strong empirical evidence.[94] Moreover, there are virtually no accepted and certainly no tested caregiver behaviors associated with enteral feedings in preterm infants, although some recent research has produced evidence for a positive effect of greater caregiver sensitivity to infant feeding during the oral phase of feeding.[84] However, more research in this area is needed before interventions of this sort can be incorporated regularly into routine caregiving in the NICU.

CONCLUSION

Remarkably little is known about mechanisms causing subtle or overt brain damage in preterm infants. Moreover, few interventions have been shown to reduce the rates of neurobehavioral disorganization and cognitive dysfunction in infants who were born preterm. This article has introduced a model of neurodevelopmental risk and protection that may be useful in further identification of risk factors as well as interventions and

caregiving approaches. Although it is tempting to endorse particular interventions to promote improved neurodevelopmental outcomes, with a very few exceptions, there is insufficient data to do so. Certainly skin-to-skin care, auditory-tactile-visual-vestibular intervention, and NIDCAP all offer advantages to the preterm infant and are arguably an improvement over "usual" caregiving approaches. However, as noted, none of these interventions address the complexity of neurodevelopment and, in particular, the lack of systematic patterning that appears to be a requirement for optimal neurodevelopmental functioning.

Future progress in improving neurobehavioral and cognitive outcomes depends on the conduct of clinical trials that examine the effect of neuroprotective interventions designed to take advantage of the preterm infant's capabilities. It is further important that the relationships among biobehavioral risk factors, interventions, and outcomes be examined such that future interventions can be developed that are tailored more specifically to newborns with varying risk profiles. The model of neurodevelopmental risk and protection proposed in this article presents 1 avenue by which these relationships might be examined and further studied.

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