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The development of potentially better practices to support the neurodevelopment of infants in the NICU

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Objective: To review the existing evidence used to identify potentially better care practices that support newborn brain development.

Study Design: Literature review.

Result: Sixteen potentially better practices are identified and grouped into two operational clinical bundles based upon timing for recommended implementation.

Conclusion: Existing evidence supports the implementation of selected care practices that potentially may support newborn brain development.
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Keywords: sleep; containment; swaddling; non-nutritive suck; newborn massage; skin to skin contact; kangaroo care; pain management; cycled lighting; noise abatement; newborn; preterm

Introduction

Neurodevelopmental care is a broad term applied to physician–nursing practices, physical environmental elements and family involvement philosophies that may favorably impact the neurodevelopment of the premature newborn. It has included promotion of positioning strategies, gentle touch, modulation of light and sound exposure, increased parental involvement, as well as an emphasis on the need to preserve sleep. There has been a recognized need to systematically address these issues.[1] The decision to implement these practices is based upon evidence derived from a rapidly evolving body of scientific knowledge. This is found not only in the medical and nursing literature, but also in the fields of neuroscience, neurobiology, neurophysiology, developmental psychology and developmental psychobiology.

The objective of this study was to review and consolidate available evidence for environment-related care practices that may support neurodevelopment in premature infants receiving care in the Neonatal Intensive Care Unit (NICU) setting. From this review, we identify potentially better practices that are bundled into an operational framework for implementation.

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Methods

From November 2004 to December 2006, five member hospitals of the Vermont Oxford Network sponsored Neonatal Intensive Care Quality Collaborative 2005, formed the physical environment exploratory group (nickname: Senses and Sensibilities), which worked to identify and implement care practices that would be potentially supportive to newborn brain development.

A working premise is that the physical environment is received and interpreted by the newborn's sensory systems. Each hospital center took a lead role in the development and implementation of care practices that involved a predominant sensory system: tactile, chemosensory, auditory and visual, and the fifth center focused on sleep preservation strategies. Coordinated by our group Facilitator (J Handyside), with input from the Clinical Expert (S Graven) and Clinical Leader (W Liu), collaboration and shared learning were emphasized and facilitated using: (1) four national Neonatal Intensive Care Quality Collaborative 2005 conferences, (2) fifteen teleconferences, (3) web-based listserv, (4) sharepoint website to facilitate document sharing, review and revision.

Steps toward this goal, patterned after previous Neonatal Intensive Care Quality Collaborative 2005 projects,[2,3] included initial review of goals and interests of each participating center, identification of a shared aim, and the evaluation and development of potentially better practices. The development of these potentially better practices is the focus of this report.

We reviewed available literature that provided the foundational understanding of brain development and the role of sleep. Supportive clinical evidence was organized by sensory systems: tactile, chemosensory, auditory and visual, and the need to develop strategies to preserve newborn sleep.

Search strategy

For the areas of interest, evidence is sought using MEDLINE (1966 to November 2006), EBM at OVID, including Cochrane

Neonatal Group of Cochrane Databases of Systematic Reviews, CINAHL at Proquest, references obtained from bibliography of articles retrieved from the primary search, previous reviews including cross references, abstracts, conferences and symposia proceedings and the group expert (SG). Journals primarily English language or translations, with both human and animal data.

The level of evidence was categorized using the Gray–Muir classification,[4] as follows:

(1) Evidence from at least one systematic review of multiple well designed randomized controlled trials.
(2) Evidence from at least one properly designed randomized controlled trial of appropriate size.
(3) Evidence from well-designed trials without randomization including single group pre-post, cohort, time series or matched case controls.
(4) Evidence from well-designed non-experimental studies preferably from more than one center or research group.
(5) Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees.

For purposes of this review, animal studies are included as level 5 evidence.

Results

A total of 16 potentially better practices were identified. These practices are bundled into two major gestational age grouping: (1) 11 PBPs with recommended implementation at 23 weeks and continued to term, (2) 5 PBPs with implementation at 31 to 32 weeks and continued to term and beyond in some cases (see Table 1).

The following is a summary of the evidence base used to arrive at the above potentially better care practices.

Processes of neurosensory development

Genetically predetermined processes. Brain organization is initially dependent upon genetically predetermined processes. This involves nerve cell division, differentiation, migration and initial alignment. These are controlled by genetic signaling, and predetermine the migration of neurons to form the embryologic structures.[5,6] This process is largely completed, except for axon targeting and some cell differentiation, before 20 weeks gestation, and probably not affected by outside sensory stimulation.

Embryologically, by the end of the 4th week of gestation, the human brain has reached the three-vesicle stage. Phylogenetically, the more primitive structures have fewer cell layers, and this ontogeny follows a caudal to rostral progression. Notably, the archicortex and paleocortex are three layered, and the neocortex is six layered. The most advanced and rostral portion is the forebrain or prosencephalon, which will subdivide into telencephalon (neocortex forms the cerebral hemispheres) and diencephalon (forms the thalamus, hypothalamus, subthalamus and epithalamus). The archicortex of the midbrain or mesencepalon forms the tectum, pretectum and cerebral peduncles. The paleocortex-derived hindbrain or rhombencephalon forms the pons, cerebellum and medulla oblongata.

From these early origins, beginning at 6 weeks gestation, there is an ongoing and systematic neuronal proliferation, with extensive axonal migration and synapse formation.[7] Brain mass increases extensively with a relatively greater growth of the cerebral hemispheres anteriorly (frontal lobes), dorsally (temporal lobes) and inferiorly (occipital lobes). There is a relatively greater growth of the outer three lamina of the six-layered neocortex, which leads to gyral formation.[6] The region overlying the corpus striatum lags in growth and forms the insula, resulting in cortical infolding and opercular formation by 33 weeks.[8] The magnitude of this growth can be appreciated on gross inspection of the brain at advancing gestational age. At 13 weeks gestation, the fetal cortex is smooth, without gyri or sulci. By 26 weeks, there is development of the central and lateral sulcus, and a rudimentary insula, with full sulcus formation by 30 weeks. The smooth surface of the 26-week-cortex is markedly different from the typical convoluted pattern of the brain at term.[7]

The human neocortex utilizes about 20 billion neurons at birth, with no further proliferation.[9] The subsequent increase in brain mass is accounted for by axonal and dendritic growth and arborization (60 to 240 trillion synapses in the adult brain) and glial proliferation. Axonal myelination begins to occur between the end of the second trimester and proceeds through 40 weeks gestation.[10] From 24 to 28 weeks gestation through the first 3 years of life, tremendous refinements and restructuring of neuronal connections occur. Early on there is a predominance of synaptogenesis, with a shift towards synaptic refinement, pruning and restructuring with maturation.[11–13] This early phase of rapid synaptogenesis is a sensitive or 'critical period', where environmental factors may have formative or detrimental influences on brain development.[6,11–17]

Once this initial configuration of neurons is established, there are two major stimulus-driven processes that are essential for the development, organization and modeling of neural circuits: endogenous or activity-independent and exogenous or activity-dependent stimulation.[18–22]

Endogenous stimulation. Research on the development of the human visual system has provided great insight into this process.[20] Endogenous stimulation originates from spontaneous firing of neurons unrelated to outside stimuli. These spontaneously firing neural circuits are mediated by the excitatory neurotransmitters acetylcholine and glutamate. Gamma-aminobutyric acid, which, with maturation, will become a primary central nervous system inhibitory neurotransmitter, early in development, functions as an excitatory neurotransmitter. This increased excitatory stimulus in

Table 1 PBPs to support brain development in the newborn

PBPs[a]	*Highest level of evidence supporting any short-term benefit*	*Any clinical trials demonstrating long-term neurodevelopmental benefit/level of evidence*	*References*
I. Full Implementation recommended for all NICU admissions beginning at 23 weeks gestation:			
T-1: Containment and body flexion (T/S)	2	No	137–154
T-2: Oral Stimulation/Non-nutritive suck (T)	1	No	155–181
T-3a: Gentle touch, hand grasping/facial stimulation (T)	3	No	184, 203–206
T-4: Decrease painful/negative stimulation (T/S)	2	Yes/3	235–257
C-1: Exposure to mother's scent (C)	3	No	284–305
C-2: Minimize exposure to noxious odors (C/S)	3	No	306–313
A-1: Noise abatement (A/S)	3	No	314–366
V-1: Minimize ambient light exposure (V/S)	3	No	225, 381–392
V-2: Avoid direct light exposure (V/S)	3	No	21, 381, 382, 384, 388
S-1: Develop strategies that preserve normal infant sleep cycles Support family involvement in care practices that promote sleep Non-emergent care provided at appropriate times to minimize the disruption of sleep (with diurnal implementation, as possible, after 30 weeks gestation).	3	Yes/3	59–128
S-2: Minimize exposure to narcotics and other medications that may disrupt or disturb sleep cycles	3	Yes/4	116, 129–136, 258–283
II. Full Implementation recommended for all NICU admissions beginning by 31–32 weeks:			
T-3b: Infant massage/diurnal implementation (T)	2	No	185–206
T-3c: Skin to Skin care (T/C/S)	1	Yes/2	209–234
A-2: Exposure to audible maternal voice/diurnal implementation (A)	3	No	367–372
V-3: Cycled lighting: minimum of 1–2 h (A/V/S)	2	No	392–425
V-4: Provide more complex visual stimulation: after 37 weeks (V)	3	No	15, 381, 382, 426, 427

Abbreviations: A, auditory development; C, chemosensory development; NICU, Neonatal Intensive Care Unit; S, preservation of sleep; T, somatesthetic/kinesthetic/proprioceptive development; V, visual development.
[a]PBPs may impact multiple developing sensory systems (T/C/A/V/S).

early development favors development of endogenous waves of spontaneously firing neural networks[21–24] also called early network oscillations[21] or giant depolarizing potentials.[23]

These neuronal discharges will originate in multiple areas of the brain and function at three levels of maturation:

(1) The initial repetitive discharge occurs early after differentiation into a ganglion cell and is associated with growth of the axon toward a target cell. This occurs very early in development.
(2) Ongoing random discharging from isolated neuronal cells, which follows the early repetitive cell firing. This will occur at different times for each sensory system and are associated with the targeting of axons from ganglion cells of the retina, cochlea, cerebellum, hippocampus, thalamus, superior colliculus and spinal cord.[21,22] They are essential for the accurate targeting of neuronal axons to the sensory receptors, that is, eye, ear, skin and other tissues to relay nuclei and thus to the cortex. They are presumably active for the somatesthetic (touch), kinesthetic and proprioceptive systems as early as 24 to 25 weeks gestation. No technology currently exists to measure this in human infants at that age.
(3) As the human fetus approaches 28 weeks gestation, various sensory and central brain systems commence synchronous ganglion cell waves and reciprocal oscillations connecting sensory organs with the cortex, thalamus, brainstem and other areas necessary for neurosensory development. In the human visual system, these synchronous waves appear with the maturation of the starburst amacrine retinal cell that coordinates the discharges of the retinal ganglion cells. Additional endogenous stimulation via pontine-geniculate-occipital (PGO) waves originating from the pons further stimulates the lateral geniculate nucleus (LGN) and the visual cortex. These endogenous waves, by facilitating accurate topographic-spatial connections from the retina to the LGN and from the LGN to the visual cortex, are essential for development of the wiring necessary for accurate transmission

of retinal images to the visual cortex. Similar endogenous neural stimulation is occurring for all the sensory systems, and this process helps to prepare the central nervous system for the introduction of appropriate exogenous stimulation.[20,25]

Exogenous stimulation. Exogenous stimulation is activity-dependent neuronal stimulation arising from sources outside of the brain that are received through the sensory systems. With the genetically predetermined programming and the influence of endogenous stimulation, the neurosensory system becomes 'primed' for exogenous input. Both endogenous stimuli and appropriate exogenous stimulation are necessary for normal neuronal development during a species-specific critical period, in humans beginning in the second to third trimester and ending at 2 to 3 years of age for the visual system,[20] Early research on the development of the visual system has demonstrated monocular visual deprivation during this critical period, can lead to profound alterations in the development of the visual cortex and its connections.[15,16] At a specific, but variable time point, each sensory system requires appropriate exogenous stimulation that cues the movement of cortical neurons into sensory-specific functional columns. Deprivation or abnormal exogenous stimulation during this critical period will potentially disrupt normal development.

Sequential theory of sensory development. Extensive animal research suggests that the timing, intensity and nature of exogenous stimulation are all important to normal neurosensory development. This research has provided the foundational evidence to support the theory that atypical and mistimed sensory stimulation play an influential role in brain development.[26,27] Sensory systems do become functional prior to birth, but this development and maturation are not simultaneous. In birds and mammals (including humans), it appears that sensory systems develop in a fixed and sequential pattern. The tactile system develops earliest, followed by chemosensory and auditory, with the visual system developing last.[28] This staged maturation coincides with typical *in utero* sensory exposures, with the uterine environment providing a more controlled and filtered exogenous sensory input.[29–31] The implication is that there is a functional reason for limiting excessive sensory stimulation during early sensory development.[27,32]

Animal studies suggest that the timing of sensory exposures may be as important to development as the type of sensory stimulation.[33–37,43] For example, auditory cues seem to have functional priority over visual ones in early development in precocial birds.[28,38–42] Term newborn infants tested at 6 months of age demonstrated an auditory dominance,[44] with a progression to visual dominance by adulthood.[45]

Atypical onset and intensity of later developing sensory experiences (for example, early or excessive visual input) may interfere with the development or function of an earlier developing system (for example auditory or chemosensory). Early or enhanced visual experiences may lead to the accelerated development of the visual system with an associated decline in auditory or chemosensory responsiveness.[36,46,47]

Some species-specific range of normal exposure exists, and deviations of exogenous stimuli above or below this range, or with atypical timing, may negatively impact or alter typical perceptual development.[47,48–51] Term newborns exposed to light with auditory pre-stimulation had a subsequent preference for lower light stimulation compared to babies who did not have increased auditory stimulation.[52] A similar study using incrementally increasing sound and light pre-stimulation, found a linear and inverse relationship.[53] Interestingly, newborns with increasing levels of intrinsic arousal had a similar inverse relationship, preferring a lower frequency of visual stimulation.[54] Preference behaviors may be associated with quantitative aspects of sensory stimulation or the level of arousal, rather than to any specific properties of the stimulus.[53,55] There does appear to be a relationship of state organization maturation to acquisition of exogenous experiences (see Role of sleep).

There is a variable impact of sensory stimuli if it occurs prior to or after birth. Chicks presented postnatal auditory and visual cues simultaneously had better responsiveness to maternal cues versus those presented one or the other, or both temporally separated.[56,57] This postnatal bimodal exposure is facilitative, but if it occurs prenatally, or too early, it may have an 'interference effect' and lead to detrimental effects later in development.[33,50,58]

Although intriguing and suggestive, these animal studies have not been established as predictive models for human brain development, and application of this research should be only in very general terms, recognizing interspecies variation. The normative ranges of acceptable sensory stimuli, as well as the exact impact of timing are not well defined in the human newborn. At this time point, we can only speculate on what constitutes an appropriate amount and timing of tactile, chemosensory, auditory or visual sensory exposure for the preterm infant in the NICU. However, it may be prudent to recognize the potential value of this compelling body of animal research, and act to minimize the early, excessive and inappropriately timed multimodal stimulation that dominants the NICU environment.

This reality of inappropriate multimodal exogenous exposures may be more effectively mitigated with the bundling of several potentially better practices.

Role of sleep in brain development

Intuitively, the relentless interventions associated with intensive care treatments will disrupt normal sleep patterns. The presence of normal sleep organization in the preterm infant may have prognostic significance for neurodevelopmental outcome.[59–61]

There is a growing body of literature that supports and elaborates upon the value of sleep in early brain development.[62]

Endogenous stimulation is critical to early directed synaptogenesis. The preterm infant at 27 to 30 weeks gestation has recognizable sleep states,[63] and this endogenous stimulation will occur primarily during rapid eye movement (REM) or active sleep (AS).[64–66,105]

After birth, in a complementary relationship with REM sleep, the importance of non-REM (NREM) sleep increases as the maturing brain receives and organizes meaningful exogenous stimulation in the form of learning or memory consolidation.[67] This relationship between REM and NREM sleep also appears to play a role in synaptic remodeling, and the ability of the brain to 're-wire' itself to adjust to various sensory exposures.

Background-sleep architecture. The development of normal patterns of sleep architecture can be distinguished by the maturation of functional stages of sleep and the temporal organization of sleep marked by an ultradian cycling of sleep states, and the shift towards a circadian rhythm of sleep and wake periods.[68]

In adults, there are five sleep stages: stage I: drowsiness; stage II: light sleep; stages III and IV: deep sleep and REM sleep. Stage I to IV sleeps are classified as NREM sleep, slow wave or quiet sleep (QS). As we progress into deep sleep, the electroencephalogram (EEG) tracing is characterized by increasing amplitude, and lower frequency and more synchronicity. During stage I, or the drowsy, wake state, EEG tracings are characterized by low amplitude, high frequency and desynchronous cortical tracings (β waves). α waves can occur during relaxed, waking periods, and are more synchronous compared to β waves. Stage II sleep is characterized by θ waves, sleep spindles (sudden increase in wave frequency) and K complexes (sudden increase in wave amplitude) on EEG tracings, whereas stage III and stage IV sleeps have a predominance of waves. Respirations are regular, and there is progressively less resting muscle activity from stage I to stage IV sleep. REM sleep is characterized by rapid eye movements. The EEG is characterized by an almost wake-like activity, with P waves from the pons and θ waves originating from the hippocampus. REM sleep gained notoriety as the phase of sleep associated with dreams. It is sometimes called paradoxical sleep because, in adults, it is marked by a high degree of brain wave activity, with diminished motor activity.

Sleep states are not as well defined in newborns, with less clarity to the EEG interpretation, and thus their identification depends more on behavioral markers. QS or NREM sleep EEG tracings have burst suppression or trace alterans pattern. AS is a more immature form of REM sleep.[68,69] In the fetus and preterm newborns during AS, there may be irregular respirations, with active movement of facial muscles (grimacing, smiling, frowning, sucking and whimpers) and limbs (twitching, tonic or writhing motions of the body, extremities and hands), as well as breathing, sucking and swallowing motions. These early motor movements during AS are consistent with an anticipatory or preparative development of muscle groups mediated by endogenous stimulation. However, by 2 to 3 months of age, this matures to a state of muscle atonia, except for ocular and respiratory muscles.[68]

With the maturation of early sleep state organization, there is a gradual change in the relationship of AS to QS and sleep–wake cycles, linked to changing arousal thresholds. With birth, there is a shift from apparent circadian entrainment *in utero*, where the fetus is cued to his mother's diurnal activity, heart rate, body temperature, and cortisol and melatonin levels, towards a predominantly ultradian cycle, with a cycling between AS and QS. These frequent and distinct sleep state cycles occur multiple times per day. These ultradian cycles shift from a predominance of AS to a relative increase in QS. Early arousal periods are sporadic and occur through out the day. With the emergence of wake to sleep transitions, the newborn is noted to have immediate transitions from wake to AS, and with maturation into infancy, these wake states transition directly to QS during the daylight periods. With maturation, there are decreasing arousal periods during sleep, longer periods of uninterrupted sleep and wakefulness, and a shift to a diurnal or circadian sleep–wake cyclity.[68–73]

Ontogenetic hypothesis. The 'ontogenetic hypothesis' theorizes that normal sleep cycles, with a predominance of REM sleep, are necessary for early brain development.[74,75]

Roffwarg observed a great need for sleep in the infant, especially REM sleep. With maturation, there is a gradual shift towards adult sleep–wake cycles, and a marked decrease in sleep requirements, with relatively less REM sleep with age.[74] This association of extended REM sleep during a period of rapid brain maturation, stabilizing to adult levels with brain maturity, is demonstrated in animals as well.[66] Human newborns have large requirements for REM sleep. A 28 to 30 weeks old infant is almost continuously in some stage of sleep, with 80 to 90% of this as AS/REM sleep. By term, the newborn sleeps only 70% of the time, with about 50% devoted to REM sleep. Young adult levels of REM sleep, about 20%, are not reached until preschool age, and gradually decrease to $<15\%$ at maturity.[68,74,76,77] Of note, whereas there is about an 80% decrease in REM, there is only about a 25% decrease in NREM sleep over the lifetime of humans. With maturation, there appears to be a shift from a predominance of REM sleep towards a balance of REM and NREM sleep states, and this emergence of NREM sleep seems to parallel the maturational stage where there is a critical need to integrate external stimuli.[66,78]

Scher found that compared to their term counterparts, there is a measurably diminished complexity to both active and QS EEG tracings of former preterm infants at comparable corrected gestational age.[79] The implication is that this progressive maturational process in the prematurely born infant is not equivalent to the normal, uninterrupted progression in term born infants, and the undefined and obvious challenges of prematurity may result in subsequent brain reconfiguration or brain plasticity.

Sleep and brain plasticity. Brain plasticity is the capacity, within genetically determined limits, to modify neuronal structure and function in response to environmental factors and stressors. Hebbian theory postulates that the strength of 'cell assemblies' or coordinated groups of neuron-to-neuron synaptic connections are reinforced through repeated simultaneous stimulation, and reduced with diminished or uncoordinated stimulation.[80] This dose–response relationship for synaptic remodeling is shaped by the nature, character and timing of our exogenous stimulations, through long-term potentiation or depression via post-synaptic glutamine receptors (*N*-methyl-D-asparate) that mediate calcium-dependent cellular processes.[14,81] These reinforced connections occur through a genetically mediated production of synapse-strengthening proteins.[82–85] This process occurs in the context of a gradual shift towards less synaptogenesis and more synaptic pruning or remodeling with maturation.[13,86]

Maquet, Smith and Stickgold[87] have compiled and summarized recent neuroscience research that supports the theory that the sleep state functions as a facilitator for consolidation of new memories into more permanent forms.[88–97] This theoretical process has been summarized by Graven and involves (1) the acquisition phase, which occurs during wakefulness; (2) the preconsolidation phase, occurring during NREM sleep, where significant memory traces are identified and transferred to the hippocampus, parahippocampal areas and the amygdala; and (3) the consolidative phase occurring during REM sleep, where these identified memory traces are transferred back to the neocortex, and permanent memory is created. This is mediated by the P-wave generator located in the pons stimulating the hippocampus-derived θ waves that in turn communicates with the neocortex.[62,67]

Animal studies. Brain remodeling will occur with environment-related exposures during critical periods of brain development. Weisel and Hubel's landmark work on the development of the visual system demonstrated that monocular visual deprivation during the early critical period led to profound alterations in the development of the visual cortex and its connections. Asymmetric development of cortical ocular dominance columns, as measured by left and right visual cortex neuronal responses to ocular stimulation reflect what is called ocular dominance plasticity.[15,16] With monocular visual deprivation, there is unilateral loss of cortical function and regression of neuronal arborization in geniculate–cortical innervations and ocular dominance column development on the affected side, and accentuated contralateral neuronal arborization.[98,99] There is also shrinkage in the size of the LGN on the affected side and compensatory increase in the contralateral LGN.[100]

How is this plasticity affected by sleep? As noted, the endogenous phasic neuronal activity necessary for brain wiring of the developing visual system occurs during REM sleep. For the cat visual system development, this endogenous phasic activation has been identified as the PGO waves originating in the laterodorsal tegmental and pedunculopontine tegmental nuclei and the locus coeruleus and parabrachial nuclei in the brainstem.[101,102] Tracts from this area innervate and influence the archicortex, paleocortex and neocortex, as well as associative intracortical tracts.

Davenne and Shaffery, using a newborn cat model, eliminated REM sleep PGO waves through ablation of the brainstem source of endogenous PGO phasic neuronal activity.[103,104] They found loss of PGO waves resulted in structural decrease in LGN volume and neuronal size.[104,105] With loss of PGO wave activity combined with monocular deprivation, there is an accentuated disparity with decreased function marked by slower and less specific cortical neuronal responses compared to kittens with visual deprivation without loss of sleep.[107,108]

Oksenberg and Shaffery[109] used a non-surgical method of selective REM sleep deprivation, by placing the monocular light-deprived kitten on a narrow platform surrounded by water. A 1 week period of REM deprivation in this fashion, results in similar enhancement of the plasticity effects of monocular deprivation.

Both kitten models provided additional evidence of the importance of REM-associated endogenous stimulation. Experience-dependent exposures such as monocular deprivation have a selective, asymmetric impact, whereas the REM sleep PGO waves are shown to have symmetric stimulation of the visual tracts.[110] This symmetric, endogenously generated neuroactivation may have a mitigating or 'protective' role in counteracting the asymmetric plasticity induced by unilateral exogenous stimulation,[109,111,112] with the risk of accentuated negative plasticity in its absence.

In addition, rats deprived of REM sleep, using both an instrumental model[113] or a pharmacological model, develop multiple adverse behavioral changes,[113–119] as well as a significant decrease in the cerebral cortex and brainstem volume.[115,116]

Neurotransmitters. The presence of catecholamines such as norepinephrine, dopamine, acetylcholine, epinephrine, 5-hydroxytryptamine and serotonin are believed to provide developmental signals, both directly and in a hormonal fashion, towards the ontogenesis of neuronal and glial cell organization.[5,120,121]

REM sleep is sustained by a balance between norepinephrine, serotonin and acetylcholine.[116,121] During sleep, new memory formation and reactivation of previous memory traces are driven by forward and retrograde interaction between the hippocampal areas, that is, CA3 and CA1 and the neocortex via the entorhinal cortex. Acetylcholine, which is in higher concentration in the hippocampus, appears to have a modulating effect on neural responsiveness, with enhancement of excitatory post-synaptic potentials and suppression of pre-synaptic inhibition (glutamatergic feedback). Electrical stimulation of the basal forebrain area results in increased synaptic release of acetylcholine

to multiple somatosensory areas of the neocortex. Through thalamo-cortical connections, visual, auditory and tactile inputs pass through the basal forebrain and may originate in the brainstem, amygdala and prefrontal cortex.[122] Norepinephine will suppress feedback excitatory synaptic transmission in the neocortex, but not the hippocampus.[123]

This cholinergic activity is markedly increased in the basal forebrain and hippocampus during wakefulness and REM sleep, and acetylcholine levels drop to one-third during NREM sleep, whereas norepinephrine levels are quite high during wakefulness and very low during REM sleep.[123,124] During NREM sleep, the diminished acetylcholine effect would release glutamatergic synapses from cholinergic suppression in the hippocampus to the entorhinal cortex, in effect, increasing excitatory feedback. Cells that fired sequentially during waking periods would have a greater tendency to fire together during NREM sleep—a 'retrieval' of memory traces within the hippocampus. During REM sleep, the higher levels of acetylcholine in the hippocampus, and lower levels of norepinephrine and acetylcholine in the neocortex would allow 'feed-forward' propagation of hippocampal waves, with relatively unimpeded spreading of this activity within the neocortex. This results in a reinforcement or re-analysis of recent waking period activity.[123] This re-analysis of memory traces would reinforce synaptic connections and facilitate the creation of permanent memories and learning. This provides a hypothetical model for the role of neurotransmitters, which is consistent with the theory of sleep-dependent memory pre-consolidation (with neocortex to hippocampal memory transfer), occurring during NREM sleep and the long-term consolidation (θ wave driven activity from the hippocampus to the neocortex), occurring during REM sleep as described by Graven[62] and Datta and Patterson.[67]

Excitatory neurotransmitters such as glutamate have been shown, in visual deprivation experiments, to mediate brain plasticity. When a glutamate antagonist blocks transmission, the negative effects of visual deprivation are also blocked.[120]

Gamma-aminobutyric acid is believed to play a critical role in brain development, first through endogenous wave generation and increasing intracellular Ca^{2+}, and subsequently by switching to an inhibitory role, providing the necessary balance of excitatory and inhibitory inputs for more complex and versatile synaptic connections.[21,23] Calcium-binding protein parvalbumin, found almost exclusively in gamma-aminobutyric acid neurons, modulates neuronal excitability and thus controls the effectiveness of their inhibitory action.[125] In a REM-sleep deprivation model, using activated cage movement triggered by EEG/EMG-detected REM-sleep, REM sleep-deprived kittens had shown downregulation of these parvalbumin-immunoreactive neurons in the LGN. This is an evidence that REM sleep facilitates the development of neuronal receptors that are associated with synaptic plasticity.[126]

Additional evidence of the role of both NREM and REM sleep on ocular dominance plasticity was demonstrated in a series of four-kitten experiments.[127] This experiment used a shaking cage technique for generalized sleep deprivation. The first group functioned as a control, and had visual cortical response testing for ocular dominance after an initial 6 h period of monocular deprivation, while kept awake. The other three groups all had the control exposure plus an additional variable exposure period, where monocular deprivation was combined with variations of sleep deprivation (combined REM and NREM), with or without additional darkness. The second group was allowed 6 h of additional sleep, in darkness; a third group was kept awake, in darkness; and a fourth group was kept awake, with light exposure. The group with monocular deprivation followed by sleep had twice the effects of monocular deprivation on visual cortical response, and the group that was kept in the dark without sleep had the least effect. Interestingly, *post hoc* analysis revealed a positive correlation between the degree of ocular dominance plasticity and the amount of NREM sleep, and a suggestive (although not statistically significant) negative correlation with REM sleep.[127,128]

Whereas REM sleep, with its associated symmetrically targeted endogenous stimulation may mitigate or dampen the impact of asymmetric visual activity-dependent events, these potentially brain remodeling effects may be reinforced or consolidated during NREM sleep.

In summary, early in brain development, endogenous stimulation, with an emphasis on synaptic proliferation, primes the developing brain for the subsequent introduction and integration of meaningful exogenous stimulation, with an altered emphasis on synaptic refinement and pruning. This integrative process occurs in the context of a maturational shift from a predominance of REM sleep to an emergence of NREM sleep with a functional balance of REM and NREM sleep (see Figure 1).

Our present NICU care practices, marked by persistent scheduled and unintended, disturbances of infant sleep, at best, are inattentive to preservation of sleep, and at worst, overtly compromise optimal sleep cycles, with potential disruption of normal brain development. Existing evidence would support strategies to preserve normal sleep in the preterm newborn.

Recommendation: For all NICU admissions, promote strategies that preserve newborn sleep.

Medications that may interfere with sleep. Narcotics and sedatives may have a significant impact on newborn sleep (*see Pharmacologic therapies for analgesia and sedation*).

Animal models for REM sleep deprivation have utilized drugs that alter monoamine activity in the brain (atropine, aldomet, clonidine, imipramine and selective serotonin reuptake inhibitors such as zimelidine).[116] Drugs that may alter central nervous system monoamine metabolism should be used cautiously.

Caffeine is a commonly used medication in the NICU, and is known to affect catecholamine levels and cyclic adenosine monophosphate. In an animal study, theophylline decreased AS

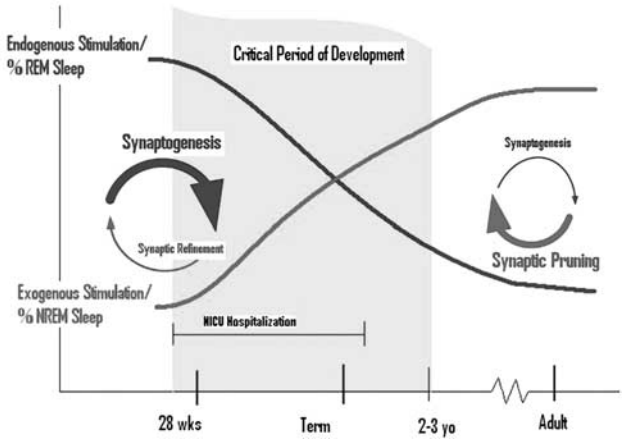

Figure 1 Relationship of endogenous and exogenous stimulation, REM/NREM sleep and brain plasticity.

and delayed the development of QS, as well as affecting the transition between sleep–wake states and active–quiet sleep, with a decrease in total sleep.[129] Contrarily, there was not any detectable adverse impact on human newborn sleep stages.[130,131] However, a small study that looked at preterm infants (at least 1 month after they had been treated with theophylline) compared to preterm infants without treatment and full-term infants, found a possible prolonged effect of theophylline upon sleep. The theophylline infants had decreased AS as well as alterations in state organization.[132]

Nonsteroidal anti-inflammatory agents such as indomethacin and ibuprofen disrupt the sleep cycle, possibly due to the inhibition of prostaglandin synthetase.[133,134]

Newborn exposure to alcohol through breast milk caused a general decrease in sleep time and a marked decrease in AS.[135] Antenatal nicotine/cigarette exposure was associated with increased obstructive apnea during AS, with an increased arousal threshold during these events.[136]

Potentially negative effects of pharmacologic interventions upon sleep should be considered prior to treatment.

Recommendation: Judicious use of narcotics and other medications that may disrupt normal sleep cycles.

Somatesthetic (touch), kinesthetic (movement) and proprioceptive (position) systems

The somatesthetic system includes several types of sensory input including touch, pressure and pain among others. The neural pathways for movement and position stimuli are intact as early as 23 to 24 weeks gestation. These systems have early endogenous stimuli for axon growth and targeting. They also set the patterns for the connections that ultimately lead to the cortex. Greater discriminatory capacity probably begins during the 28 to 32 week gestational age time period.

The nerve receptors for touch for the face (especially the lips and the perioral area), the palms of the hands (especially the fingers) and, to a lesser degree, the soles of the feet and toes are organized to provide information related to shape, texture and identity of objects while the rest of the body is organized to transmit feeling. Early endogenous and exogenous stimulation is needed to develop the topographical relationship and location of sensation.

The endogenous stimulation related to axon growth and targeting should be well advanced by 23 to 24 weeks and the need for gentle exogenous stimulation would appear to be a part of the expected progression of the development of the touch system.

Containment/body flexion. The *in utero* environment of the fetus provides somatesthetic, kinesthetic and proprioceptive feedback. Swaddling and containment of the infant with general flexion of the extremities and trunk is a general approximation of this effect. Swaddling has a long historical basis in practice.[137] It is a means to promote sleep with decreased awakenings during QS,[138,139] and longer periods of REM sleep.[140] It also appears to improve self-regulation, diminished stress response[141] and a decrease in arousal level,[142] including decreased crying,[143–145] and may promote neuromuscular development in the preterm infant.[146] Diminished pain response has also been cited as a benefit of swaddling.[147,148] For well babies, it has been promoted as a means to promote the supine position and decrease the risk of sudden infant death syndrome.[149] There is no evidence of long-term neurodevelopmental benefit from this intervention.

In the infant swaddled at home, there has been a risk of overheating with swaddling, especially if the head is also covered.[150,151] Tight swaddling has the potential to interfere with normal respiratory effort.[140] A retrospective case–control study from Turkey and China reported increased risk for pneumonia in infants who were swaddled for at least 3 months.[152] Swaddling technique that positions the hips in adduction, with leg extension may potentially have orthopedic consequences.[153,154] These reported events occur primarily in the outpatient population. There have not been any hospital-based reports of morbidity with this practice.

Recommendation: Starting at birth, provide containment and body flexion of the newborn.

Perioral stimulation and non-nutritive sucking. Gentle touch, hand grasping and facial stimulation are all of importance for the refining of the topographic spatial relationship between sensory nerve endings and the cerebral cortex. Nerve receptors for touch for the face (especially the lips and perioral areas) require early endogenous and exogenous stimulation to develop topographical relationships and location of sensation. The brain must build patterns to recognize spatial orientation and character of touch on the body. The exact timing, amount and frequency are not clearly established.

The infant may demonstrate rudimentary components of sucking and swallowing by 28 weeks gestation.[155] At about 32 weeks gestation, an infant will begin to display bursts of sucking, and by 34 weeks a rhythmic suck, swallow and breathe pattern is developing.[156–161] Non-nutritive sucking will transition towards more effective nutritive sucking, concurrent with state of alertness and increasing gestational age.[162]

Non-nutritive sucking with pacifier use may facilitate the transition to effective nutritive sucking at 32 to 34 weeks gestation.[163–166] This may be related to improved strength and coordination of the sucking process[166,167] and pacing of feedings will help with this transition.[168]

Non-nutritive sucking has been associated with improved weight gain. One postulated mechanism is a stimulation of digestive and anabolic hormones, although measurable hormonal differences have not been demonstrated.[169]

Non-nutritive sucking with oral support[170] is associated with positive changes in behavior including enhanced physiologic stability,[171–173] a more alert and receptive behavioral state for feeds[174,175] and diminished signs of stress[176] and improved pain response.[177]

Systematic reviews of experimental evidence for the practice of non-nutritive sucking have found a beneficial effect on length of stay and response to pain, but did not find consistent benefit involving behavioral states, sucking improvement, gastric emptying or weight gain.[178–180]

No harmful short-term effects have been demonstrated.[178] Although there have been concerns that the use of a pacifier as an instrument for non-nutritive sucking may result in earlier weaning from the breast, this was not significantly demonstrated in a randomized clinical trial.[181] There are no data on long-term effects of this practice.

Recommendation:

- At 23 weeks, provide perioral stimulation as tolerated.
- At approximately 32 to 34 weeks gestation, assess nipple readiness with non-nutritive sucking, with transition from non-nutritive to nutritive sucking.

Tactile stimulation: gentle touch, infant massage and kangaroo care. The focus of many groups studying touch and its role in NICU care is to offer gentle touching, holding and stroking as a part of comfort measures and human skin to skin contact.

From 30 weeks and beyond, the infant should begin to discriminate between types and sources of touch stimuli. Positive touch involves various types of infant-caregiver interaction including gentle handling, infant massage and kangaroo care.

Infant massage, like swaddling has historical roots that can be traced to ancient China, Africa and South America, but has gained attention in modern practice only in the last 20 years.[182,183] Gentle human touch is perceived as a simpler, less arousing and more easily implemented form of human touch, and may be tolerated by smaller preterm infants,[184] although selective use of infant massage does appear safe.[185]

Massage in preterm infants has shown significant[186–192] or trends toward[193,194] improved weight gain, and decreased length of stay.[187,192] Weight gain may be mediated by increased nutritional intake[195] and/or through increased vagal activity and gastric motility.[196,197] These infants also demonstrated increased heart rate, improved autonomic stability,[198] and increased range and regulation of behavioral states[186,190,199,200] with decreased stress behaviors.[190] The variations in physiologic measures and behavioral observation are interesting in that massage may have a stimulatory effect on specific activity of the sympathetic nervous system. Kuhn *et al*.[201] found an increase in urinary norepinephrine and epinephrine with unchanged urine dopamine, cortisol and serum growth hormone levels.

There may also be a beneficial effect on bone mineralization.[202]

Massage has been associated with a shift from less total sleep, towards more periods of drowsiness[188] and post-massage sleep may be increased.[193]

The use of gentle touch has been associated with lower levels of AS, motor activity and behavioral distress, but no differences were seen in weight gain or behavioral organization.[184,203] It did not have the stimulatory effect on vagal activity as noted with more active massage, nor any measurable benefits, but was well tolerated and safe.[204,205]

The Cochrane systematic review acknowledged preterm infant massage does improve weight gain by 5.1 g day^{-1} and decreases length of stay by 4.5 days, with a slight benefit on postnatal complications and weight gain at 4 to 6 months. They did not feel there was evidence of benefit with gentle touch.[206] The evaluation of strength of evidence has been limited by flaws in study design.[206,207]

There may be positive effects of this activity on maternal well-being as well as maternal: infant bonding.[208] Although there is no evidence of long-term benefit nor morbidity with infant massage or gentle human touch, potential risks do include physiologic instability in infants who may have poor tolerance of touch, and the potential for increased cost allocation for clinical time spent by nursing or occupational therapy.[206]

Kangaroo care/skin-to-skin contact. Originally reported out of Columbia South America, kangaroo mother care was introduced as an inexpensive and readily available method for providing thermoregulatory care to premature infants.[209,210]

There has been early concern that spontaneously breathing premature infants might be at higher risk for physiologic instability.[211] However, extensive evidence has established its safety for use in premature infants as an intervention that promotes neurobehavioral development,[212–215] with recommendations for implementation in physiologically stable newborns or greater than

33 weeks gestation.[216] A systematic review has demonstrated a decrease in clinical morbidity and improved weight gain, although criticisms of study design still do not allow for a recommendation for implementation.[212]

Kangaroo care/skin to skin contact improves newborn state organization, and perceptual-cognitive and motor development.[214,217–219] It may improve physiologic stability,[216,220–222] with lower infant activity level and diminished signs of discomfort, pain or stress, although salivary cortisol as a marker of stress suggested variable infant stress response.[222–224]

Infants demonstrate more mature sleep patterns with decreased periods of arousal and longer periods of QS and less AS,[214,217,218,222,225] and significantly decreased periods of arousal during QS

There have been conflicting reports of improved weight gain and decreased length of stay[226] as well as no demonstrable difference.[220,222,227]

Maternal benefits include improved parental infant attachment, improved maternal mood including feelings of self-confidence and less stress,[219,220,223,228] increased knowledge and comfort with their infant, increased maternal milk production and breast feeding.[229]

Implementation of kangaroo care in third world countries seem to demonstrate decreased mortality[230] as well as decreased length of stay and cost.[229]

One-year follow-up studies are also conflicted. Some have demonstrated improved head growth and longer period of breast feeding, higher intelligence quotient that are more pronounced in the smaller, sicker premature infant[231] and improved Bayley scores,[232] whereas others found no difference in developmental indices.[226,233,234]

Recommendation: *23* to *30 weeks*

- Encourage gentle touch: hand grasping and facial stimulation.
- Kangaroo care as conditionally appropriate and physiologically tolerated by neonate as assessed by nursing and medical staff.

31 to 32 weeks gestational age and beyond:

- Continue to provide gentle touch stimulation of different areas of the body including the face, hands and chest.
- Consider infant massage as tolerated; diurnal implementation
- Kangaroo care as conditionally appropriate and physiologically tolerated by neonate as assessed by nursing and medical staff.

Avoidance of painful/stressful stimulation. The management of pain (analgesia) and agitation (sedation) require both non-pharmacologic and pharmacologic interventions. However, pharmacological therapies for the management of newborn pain remain an area of therapeutic ambivalence.

The International Association for the Study of Pain has defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[235,236] Stress can be defined as 'a physical, chemical or emotional factor that causes bodily or mental tension and may be a factor in disease causation'.

At 23 weeks gestation, the neuronal connections from the skin and extremities and the brain are intact, and allow for nociceptive responses to pain. However, the maturation of the more complex thalamocortical connections, as reflected by somatosensory-evoked potentials with distinct, constant components are not noted until 28–30 weeks,[237] and this suggests that although a nociceptive response to noxious stimuli may be present at 23 weeks, cortical integration and discrimination of this stimuli as painful may evolve over a time period of 23 to 28 weeks.[238] Although of academic interest, this distinction between nociceptive response and conscious perception should not temporize the clinical recognition and management of noxious stimulation.

Whereas gentle exogenous stimulation would appear to support the development of the tactile system, noxious stimulation is inappropriate and potentially disruptive. Repetitive painful or noxious stimulation has negative effects on development. This has been discussed extensively in the literature, and may lead to behavioral abnormalities and alterations in subsequent response to pain, as well as potential emotional or behavioral disability.[239–256]

The recent AAP position statements has consolidated the available evidence and establishes a consensus recommendation to recognize that the prevention of pain in the neonate should be a goal of all caregivers, and strategies should be developed to prevent and manage pain in the newborn.[257]

Recommendation: Decrease exposure to painful/negative stimulation.

Pharmacologic therapies for analgesia and sedation. High catecholamine levels are an indication of stress and have been associated with neonatal death.[258] The use of morphine decreases catecholamine levels in ventilated newborns.[259,260] These findings and anecdotal opinions have been the basis for recommendations for the use of narcotics and sedatives in the management of the sick newborn.

However, there are risks with narcotic and sedative exposure. The use of midazolam for sedation has not shown measurable benefit, with increased risk of intraventricular hemorrhage and death.[261,262] In addition, continuous narcotic drips have little or no measurable impact on pain mitigation.[263–265] Fentanyl has been associated with hypothermia, chest wall rigidity,[266] and both morphine and fentanyl lead to increased length of stay associated with narcotic dependence.[267] Morphine has been associated with hypotension[268] and prolonged ventilatory support.[261,269] Increased ventilator days have been shown to be an independent risk factor for neurodevelopmental delay.[270,271] Although in a study comparing infants exposed to morphine (with and without paralysis) to infants who received paralysis alone, 5 to 6 year

follow-up data did not detect measurable neurodevelopmental deficits with morphine infusion.[272] The opiate-addicted newborn, an approximated model for narcotic exposure in the preterm infant, has clear long-term neurodevelopmental deficits including visual-motor disturbances, cognitive delay and learning disabilities.[273]

Narcotics may also have a developmental risk due to detrimental impact at a cellular level. Human fetal neuronal and microglial cells exposed to narcotics sustain increased apoptosis.[274] Animal studies have shown that morphine infusions will disrupt neuronal development and proliferation,[275,276] will downregulate μ-opioid receptors in the rat hypothalamus,[277] and decrease dendritic length[277] and arborization.[278,279]

Morphine may decrease both REM and stage III and IV NREM sleep, while increasing stage II NREM sleep.[280] Phenobarbital was shown in an animal model to decrease total REM sleep.[281] Selective serotonin re-uptake inhibitor medications (desipramine, zimeldine, clomipramine) have been used to achieve an animal model for REM sleep deprivation.[114,119]

Narcotics and sedatives including morphine, phenobarbital and diazepam alters the preterm newborn EEG tracing with a depressive effect.[282,283]

Awareness of the potential negative impact of these pharmacologic therapies on neonatal sleep and brain development, should be part of a considered decision to utilize pharmacologic therapies to relieve pain and stress. Non-pharmacologic options should be considered first. When pharmacologic treatment is perceived to be beneficial, re-assess this need on a regular basis seeking to minimize long-term exposure.

Recommendation: Minimize exposure to narcotics and other medications that may disrupt normal sleep cycles.

Chemosensory/olfactory (smell)

Exposure to mother's scent. Four major anatomic areas are responsible for human smell: the olfactory system, the vomeronasal organ, the trigeminal nerve and the terminal nerve. They all interact to provide varying sensitivities to chemostimulants. The vomeronasal organ is designed to function primarily in late fetal life, and may lose function prior to birth, as it is not detected in adults. The olfactory system is clearly functional by 28 weeks gestation, with the trigeminal nerve and vomeronasal organ effective prior to 24 to 25 weeks.[284]

The newborn infant has an inherent preference for amniotic fluid odors, breast milk and their own mothers' odor signature.[284–294] Within days after birth, olfactory preferences seem to be reinforced by exogenous cues associated with the mother's unique body odor and breast milk characteristics,[295–300] which may be translated into improved non-nutritive sucking.[301,302]

These familiar odors also seem to have an adjunctive calming or soothing effect compared to non-familiar odors or no odors during venipuncture or heel lancing procedures,[303,304] with the stress of maternal separation or as a soothing tool.[302,305]

There are no reported adverse effects of exposure of mother's scent to the newborn, although operational factors related to infection risk and cost may need to be considered.

No long-term outcome data are available.

Recommendation: Encourage exposure to mother's scent.

Avoidance of noxious odors. As noted above, the human fetus does have the ability to receive, integrate and postnatally utilize the memory of familiar chemosensory inputs obtained *in utero* and does demonstrate a discriminatory response to unfamiliar environmental odors. Presumably, noxious olfactory stimuli would interfere with meaningful odors, and has been shown to increase mortality, with nutritive maladaptation in rat pups, an animal species strongly dependent upon early olfactory cues.[306] Premature newborns also have a discriminatory sense, with a differential physiologic response to positive and negative odors.[307–310] possibly altered by chronic *in utero* stress.[311] Marlier *et al*.[312] demonstrated that vanillin, a specific olfactory nerve stimulant did have a positive impact on severe apnea in premature infants. Interestingly, the greatest effect occurs during AS, a period of greater respiratory vulnerability.[313]

Existing experimental evidence supports the theory that *in utero* olfactory stimuli influence neonatal preferences, and these predilections may be altered by olfactory exposures in the early neonatal period. Thus, it would seem reasonable to increase our awareness of the newborn's olfactory environment, and to limit their exposure to excessive olfactory irritants. However, the long-term implications for this exposure and the consequences of olfactory remediation in humans are not clear at this time point.

Recommendation: Minimize exposure to noxious odors.

Auditory system

Noise reduction. The auditory system has completed the connection between the cochlea and brain stem by 24 to 25 weeks gestation, and to the temporal lobe and the auditory cortex by as early as 30 to 31 weeks gestation.[314–316] Clinical observation suggests the fetus responds to sound as early as 20 to 26 weeks gestation.[316,317] The *in utero* environment of the growing fetus is exposed primarily to low frequency sound with filtering of high frequency noise,[318–322] with sounds above 500–1000 Hz attenuated by 20 to 50 dB.[320,322,323] Animal studies suggest that the hair cells of the developing cochlea are susceptible to damage by intense low frequency sounds.[324–326] Premature delivery exposes the infant to both low and high frequency sound without the protective noise attenuation of the mother's body. Although hearing loss secondary to excessive noise is well documented in adult humans,[327] the effects on the fetus and premature infant are not as clear. Some studies suggest fetal vulnerability to excessive noise, with increased risk for hearing loss.[328–331]

Noise levels in the NICU have been shown to be excessive and chaotic, both in the incubator as well as in the ambient environment.[332–338] Published measurements of sound levels reported in NICUs have used various methodologies with variable results[339–343] and uniformly report sound pressure levels above the optimal recommended for new or renovated NICUs.[344]

Studies demonstrating the clinical effect of sound are limited to animal models, or small non-randomized, case–control or observational designs, with wide variations in measurement technique and sound levels,[345] Animal research suggests that early exposure to sustained moderate noise may delay normal auditory development.[331] The physiologic impact of noise on the newborn infant has been summarized,[339,345] and these studies demonstrate variable relationships between sound intensity and immediate physiologic parameters. These include heart rate,[346–351] blood pressure, respiratory rate,[346,352–354] induced arousal with increased intracranial pressure[336] and possible stress-induced effects on the neuro-endocrine system.[355,356] Compared to term infants, the preterm infant appears to have a lower threshold for noise-induced arousal,[358] with less habituation[357] and sleep is clearly impacted by excessive noise levels.[359,360] Some of these effects may be mitigated with strategies to decrease noise.[361,362]

Excessive and chaotic environmental noise impacts negatively upon individual staff attention, inter-staff communication and risk of medical errors.[363] Unit design may mitigate some of these effects.[339,340,343,364,365]

Well-designed studies are needed to clearly demonstrate the immediate and long-term impact of sound on the newborn infant. Existing evidence does not dictate the optimal acoustic environment for the growing preterm infant in the neonatal intensive care setting. However, based upon animal and clinical research as well as developmental theory, weighed against the lack of evidence to justify maintaining present noise levels, it is reasonable to seek a quieter NICU environment, with the goal of prolonged periods of undisturbed sleep, as well as providing an environment that allows for audible maternal voices, and providing an improved and safer work environment for staff. Present consensus opinion establishes reasonable goals for the acoustic environment of the NICU.[344,366]

Recommendations: Minimize noise levels in the NICU

- Standardize method for noise assessment
- Unit design should seek compliance with the new Standards for NICU Design.[344]

Exposure to mother's voice. The 31 to 32 week gestation infant is capable of hearing and distinguishing speech sounds,[367,368] and this is the beginning of language and speech development. In this environment, the lower frequency component of the mother's voice is audible against this low sound level background.[321,369,370] This *in utero* exposure to maternal speech is believed to be relevant to facilitating subsequent speech and language acquisition.[368,371–377] The infant can learn and distinguish different phonemes by 35 weeks gestation.[374] Auditory signals transmit pitch, intensity and pattern to provide the exogenous stimulation necessary to develop a neocortical tonographic relationship with the cochlea, and these patterns of human speech and musical patterns are learned by the fetus between 31 and 40 weeks. The term infant will discriminate and prefer the mother's voice.[368,372,374–380]

Infants, compared to adults, are more easily distracted by extraneous noise, and the temporal processing is also slower.[372] To hear and learn human speech, sounds and patterns as well as simple musical melodies, the background noise should be kept at a low enough level to allow for the infant to discern the mother's voice. This appears to be an essential process in the development of the auditory system as well as language. This process continues after term birth.

Recommendation: 31 to 32 weeks gestational age and beyond.

- Encourage audible exposure to mother's voice; diurnal implementation.

Visual system

Ambient light exposure. The development of the visual system has been well summarized.[381]

The ganglion cells of the retina require endogenous stimulation beginning prior to 24 weeks gestation. The synchronous waves begin at 30 to 31 weeks and are essential for pruning of peripheral or unneeded connections and the development of clear accurate topographical relationships between the retina and the visual cortex. The synchronous waves stimulate the organization of the LGN, the superior colliculus and the formation of the ocular dominance columns in the visual cortex. These formative retinal waves diminish once exogenous light stimulation begins to occur.[20] The growing fetus needs no exogenous light stimulation prior to 40 weeks.[381]

When REM sleep is constantly interrupted by excessive lighting or when the eye is subjected to a constant flicker of light, the synchronous waves do not occur, and there is interruption of the normal development of orientation and directional ocular dominance column formation.[19,20,382] Protection of REM sleep and avoidance of light flicker may be essential for the development of the appropriate visual neural architecture.[21,381,382] This appears to be critical after 30 to 31 weeks but may be earlier.[381]

Standard lighting in an NICU has been reported to range from 37 to 50 lux during the nighttime hours and 192 to 890 lux during the daytime.[383–385] It is not uncommon for the infant's ambient illumination to be beyond the value currently recommended by the New Standards for Newborn Intensive Care Unit Design.[386] Often the youngest and sickest infants are exposed to the highest levels of light, such as during phototherapy (approximately 3000 lux)[387] or for medical assessment and procedures.

A preterm infant's ability to protect their eyes is complicated by their physiologic immaturity. The pupillary light reflex, which controls the amount of light entering the eye, is highly correlated with gestational age. Robinson and Fielder[388] found that no infant less than 30 weeks gestational age at birth had a pupillary reflex. At 34 weeks gestation, 86% had a light reflex and at 35 weeks gestation all infants had the reflex present. The investigators also found that babies, who had no reflex, also had a larger pupillary diameter. Therefore, the very immature baby receives a larger retinal light dose than their older counterparts.[388] Direct ambient light has a negative effect on the development of a preterm infant's visual neural architecture. There is evidence that babies are unable to protect their eyes from constant overhead light. The eyelids of premature babies are very thin, and for several weeks, babies may not be strong enough to keep their eyelids closed at all times. The amount of light transmission is increased in the more premature infant.[384] Babies are cared for part of the time in the supine position, and the presence of direct overhead lighting would leave then unable to avoid this potentially unpleasant stimulus at least some of the time.

A *post hoc* analysis of a randomized clinical trial looking at the effect of skin-to-skin care on sleep found that high ambient light was associated with a slight decrease in QS. With ambient light levels <240 lux, there was a significant increase in QS.[225]

Looking at the potential impact of reduced light exposure, Roy *et al*.[389] randomized infants to standard management or early ocular occlusion. They found that early ocular occlusion does not impair future central visual development. Therefore, the recommendation to minimize but not eliminate ambient illumination should not negatively impact this particular visual outcome. Blindfolded infants have lower activity levels and more stable respiratory patterns.[390] When infants do begin to visually engage with the environment, lower intensity light tends to result in increased proportion of time spent with the eyelids open and the amount of time spent in the awake state.[391]

Recommendation:

Provide exposure to low ambient light.

- Standardize method for obtaining light measurement
- Unit design should seek compliance with the New Standards for NICU Design.[344]

Avoid exposure of the infant to direct ambient lighting

- Use indirect lighting except for procedures when lighting can be used with appropriate shielding of the baby's eyes.

Visual: cycled lighting. The preterm newborn has only short periods of arousal interrupting almost continuous sleep, decreasing to 16 to 17 h day^{-1} of sleep by term. This sleep is characterized by an ultradian cyclicity with a predominance of AS in the preterm infant, and a gradual shift to a balance of QS and AS by term. With birth, and exposure to light, there is an emergence of circadian rhythmicity, marked by increasing periods of daytime arousal and a progression to definite diurnal sleep–wake cyclicity by 7 to 16 weeks chronologic age.[392]

Infants and their families are generally exposed to cycled lighting in the home environment with lights off at night and natural light exposure from windows during the day. Intensive care nurseries lack this normal pattern of cycled lighting when bright lights are used continuously to improve observation of the babies.

Some modern NICUs have a chaotic lighting pattern, with wide variability in lighting characteristics, neither constant nor circadian in nature.[393] Neither continuous dim nor continuous bright light has been demonstrated to be optimal for the development of preterm babies. Exposure to continuous dim lighting has been favored as simulating the dark conditions *in utero*.[394] However, reduced lighting as part of the Neonatal Individualized Developmental Care and Assessment Program intervention has no measurable clinical benefit[395] and outcomes are not improved when babies are exposed to continuous dim lighting from birth. Continuous bright lighting has been linked to increased incidence of retinopathy of prematurity.[396] When light exposure to babies was reduced by having them wear goggles until 31 weeks gestation or 4 weeks after birth, there was no reduction in the severity or incidence of retinopathy of prematurity.[397,398] On *post hoc* analysis, this continuous darkness did not demonstrate any differences in weight gain or improved clinical morbidity.[399]

The importance of lighting on circadian rhythms, and evidence that this circadian rhythmicity is developing in preterm infants, suggest a need to consider the potential benefits of cycled lighting.[400,401] Circadian cycles are those which exhibit a periodicity of about 24 h. These rhythms are generated by an internal timing system. Input pathways (including the retinohypothalamic tract from the eye) bring signals to the suprachiasmatic nuclei, which is thought to be the location of the biologic clock.[402] This may be coordinated with a retina-based light-sensitive receptor that interacts with the suprachiasmatic nuclei.[403,404] Observations of fetal activity suggests a circadian rhythm as early as 22 weeks gestation.[405] This *in utero* effect may be mediated by maternal activity as well as diurnal variation in maternal cortisol and melatonin.[400,406] These maternal cues are lost once the baby is born.

After birth, light becomes a significant signal that entrains circadian cycles. The input of light from the retina to the suprachiasmatic nuclei synchronizes or resets the oscillations of the clock to the 24-h cycle. The effect of lighting cycles on adults has been extensively studied but little is known about how lighting cycles affect infant development.

Does circadian entrainment occur in the premature infant? Light entrainment of circadian rhythms has been demonstrated in

animals.[407,408] Studies in newborn infants as early as 28 weeks gestation have demonstrated some aspects of circadian rhythmicity in body temperature,[401,409–412] respiratory pause frequency[411] and blood amino-acid level measurements.[413] Using amplitude integrated EEG, cyclic changes in sleep state have been identified in preterm infants as early as 27 weeks gestation, with onset at 6 days of age.[414] With a combination of EEG recordings and REM counts, sleep state cyclicity was detected in 72% of 25 to 30 weeks post-conceptional age preterm infants.[415] Using actigraphy as a measurement of rest-activity patterns, infants born at less than 32 weeks gestation and exposed to low intensity (200 lux) cycled lighting between 32 to 34 weeks postmenstrual age demonstrated light entrainment of circadian rhythms as early as 37 weeks postmenstrual age.[416]

When compared with infants in continuous lighting, babies in cycled lighting slept more, spent less time feeding and gained more weight,[417] and during the darker periods, had lower activity levels and more stable respiratory rates,[418] as well as increased sleep states and decreased cortisol levels.[419] When lighting was reduced at night, weight gain, ventilator days, length of stay and scores on the Brazelton motor cluster were improved at the time of discharge.[420] Brandon *et al*.[421] found that babies born at less than 31 weeks gestation exposed to cycled light, had improved growth while hospitalized.

Are these differences the result of continuous light or other factors such as bundled staff interventions and modified activity? Mann's study did involve simultaneous modification in light and noise levels. Heart rate and sleep may take on a more ultradian periodicity associated with feedings and staff care interventions.[392] In one study that demonstrated benefits to cycled lighting, there was no difference in staff behavior as measured by the frequency of staff interventions.[420]

Other studies have failed to demonstrate that weight gain is improved when babies are exposed to cycled lighting,[416,422] nor detected accelerated maturation in sleep–wake progression.[424]

Although there is a progressive shift towards sleep–wake circadian rhythmicity with maturation, this may occur independently of the amount of ambient light exposure, suggesting circadian entrainment may occur based upon an endogenous, exposure-independent pacer mechanism.[423,424] Presently, it is clear that the newborn does not achieve an obvious circadian pattern until 3 to 4 months chronologic age, and that, prior to term birth, there is an *in utero* entrainment.

However, there is no evidence that cycled lighting is harmful, and some evidence it may be beneficial. There is still limited evidence regarding the optimal light levels needed to entrain the circadian rhythms in preterm human infants, the age at which cycled lighting should be introduced, and the time necessary to be exposed to higher levels of light 'or if', or to what degree, the optimal development of the internal circadian rhythm is dependent upon continued external entrainment.

There is a normal developmental progression in the ultradian balance of AS to QS that parallels the maturation of the circadian sleep–wake rhythm, and this also may have some biorhythmic entraining function.[69] Other aspects of routine care practices with temporally related activity and auditory stimulation, timing of feeds and even the timing of expressing of mother's breast milk[425] may also function as non-visual circadian cues.

Recommendations: 32 weeks gestation and beyond

- Provide cycled lighting for infants: minimum of 1 to 2 h during the daytime
- When providing infant care, recognize the potential importance of non-visual entrainment factors for circadian entrainment.

More complex visual stimulation. The exogenous visual experience becomes important after the infant reaches 38 to 40 weeks gestation, and is vital to resolution and refinement of retina to cortex connections, development of additional ocular dominance columns, and of directional columns of the primary visual cortex.[15,382,426,427] These need to include columns for lines, patterns, movement, direction and color perception. For these to occur optimally, the infant requires adequate indirect illumination for visualization of objects or images, ability to focus (focal length of 10 to 12 inches) and attend (not sedated) to the human face and other objects, novelty or change, movement and introduction of color (after 2 to 3 months).[381]

Recommendations: After 37 weeks, provide more complex visual stimulation.

Discussion

We have summarized the evidentiary basis for these general recommendations for environment-related care practices that potentially support neurodevelopment, with an emphasis on the 'potential' and not definitive benefit. We have recommended a 'bundled' approach, with simultaneous implementation of several care practices that are justified by variable levels of evidence. This is a lower standard when compared with the Institute of Healthcare Improvement application of bundled practices that require a level 1 evidence of benefit. The Institute for Healthcare Improvement utilizes bundles of care, because they are all necessary and all sufficient, more effective as a group than if implemented separately. Removal of any one of these practices may lessen the ultimate benefit.[428] Our reasoning for the bundled implementation of these recommended practices is the same, but the anticipated degree of benefit is more uncertain.

This is an evolving science, with only partial answers that demand further questions. Much more clinical correlation is needed in our understanding of the importance of sleep. The formative role of AS (associated with endogenous stimulation) and the later emergence of the integrative role of QS (with exogenous stimulation), as well as the postnatal development of circadian

wakeful periods, mesh in an epigenetic fashion with a normal progression from the limited and selective exogenous stimuli of the *in utero* environment, to delivery at term, with expected and necessary multimodal exogenous exposures. Alterations in this normal progression may have some predictive relationship to future neurodevelopment.[60,61] Borghese *et al*.[429] demonstrated sleep state cyclicity in 41% of preterm infants at 36 weeks gestation, and found that this earlier emergence of QS was negatively correlated with neurodevelopment at 6 months of age using the Bayley Scales of Infant Development. This is a fascinating insight given that QS may have a facilitative role in the integration of exogenous stimuli. What is the normal shift in the fetal AS/QS patterns during this third trimester period? How is this normal maturation of AS/QS cycles altered with preterm birth? In the context of appropriate or inappropriate exogenous stimulation, are these alterations adaptive or maladaptive?

There are many short-term consequences of our potentially better care practices, but the ultimate evidence of benefit is measurable long-term neurodevelopmental improvements. As noted in our review, there are few high-quality long-term studies evaluating the effect of developmentally supportive care practices.

A recent systematic review of clinical trials found limited benefit from broad developmental care interventions, with many studies flawed by concerns regarding study design and small sample size.[430] Of special note is the implementation of the Neonatal Individualized Developmental Care and Assessment Program or individualized developmental care. This is a theory-based, highly organized and comphrehensive approach towards minimizing infant stress utilizing an individualized strategy to optimize infant self-regulation. It involves resource-intensive training to achieve advanced-level developmental specialists. Although the participating centers did not implement this approach, there is a shared belief that reduction of infant stressors, and facilitation of the infant's own ability to self-regulate within his environment is supportive of normal brain development. Individualized developmental care has been shown to decrease ventilator days, with improved weight gain and decreased length of stay,[393,431] and improved behavioral performance.[432] It was not found to improve developmental outcomes nor alter sleep at 2 years of age,[394] nor, in one meta-analysis, was existing evidence strong enough to warrant recommendation for treatment.[433] However, a more recent randomized, three-center clinical trial of individualized developmental care for infants less than 1250 g did demonstrate more rapid transition to full enteral feeds, shorter length of stay with improved weight gain and enhanced self-regulatory functioning.[434] Of interest is that there were no differences in relative measurements of light and sound between treatment and control groups, although the study was not designed to look specifically at these factors. The potentially beneficial effects of diminished stress during critical periods of development may reflect multiple strategies with overlapping beneficial pathways. For example, excessive noise and lighting may also contribute to stress. One may speculate that optimization of these additional factors might be additively beneficial.

It is challenging to demonstrate strong evidence that changes in existing environmentally related practices result in measurable improvements in long-term developmental outcome. Common medical conditions such as chronic lung disease, apnea, hypothyroxinemia, inadequate nutrition and essential fatty acid deficiency, as well as hyperbilirubinemia all may contribute to poor long-term outcome.[435] Major neurologic injury such as periventricular/intraventricular hemorrhage will clearly increase the risk for neurodevelopmental compromise. This vulnerability is due in part to the early role of the germinal matrix as a source for neuronal precursors, largely migrating to appropriate cortical sites prior to 20 weeks gestation. After 20 weeks gestation, this region provides primarily glial precursors that will differentiate into oligodendroglia and astrocytic precursors, which are necessary for neuronal myelination and cortical brain development.[436] These medical factors, concurrent with environmental factors, combine to form a matrix of causality, reflected in grey and white matter alterations, leading to a long-term outcome effect.

About 10% of very low birth weight infants develop cerebral palsy, and fully 50% develop more subtle cognitive or behavioral deficits that may not be recognized until school age.[435,437–445] Of these infants, only 3 to 5% are diagnosed with classic cystic periventricular leucomalacia.[446] Follow-up studies of premature infants demonstrate that there are many infants without ultrasound evidence of abnormality who continue to demonstrate significant cognitive and behavioral deficits. Laptook *et al*.[271] found that nearly 30% of extremely low birth weight infants with a normal cranial ultrasound had either cerebral palsy or a low mental developmental index. Schmidt *et al*.[447] found that although prophylactic indocin significantly decreased the incidence of severe intraventricular hemorrhage, there was still no difference in 18 months follow-up for cerebral palsy or moderate to severe cognitive deficits. More recent neuroimaging technology has demonstrated that in addition to periventricular/intraventricular hemorrhage and periventricular leucomalacia, there is a more diffuse non-cystic white matter involvement, sometimes associated with ventriculomegaly, that is present in 20 to 50% of very low birth weight infants, and is also associated with neurodevelopmental compromise.[446,448–451] A magnetic resonance imaging study of a small group of premature infant between 28 to 33 weeks gestation, without ultrasonographic evidence of neurologic injury, found they still had a loss of white matter volume, but with a relative increase in grey matter volume.[452]

In addition to the vulnerability of cerebral white matter in premature infants, there appears to be evidence that cerebral

neuronal structures are also affected. Some studies of these at risk infants demonstrate abnormality in gyral grey matter development, marked by decreased gray matter volume.[453–456] This loss of grey matter may reflect neuronal cell loss and diminished dendritic growth and synaptogenesis.[457,458] Diminished head growth has been associated with cognitive delay and behavioral deficits.[459,460] Recent studies have demonstrated that this cognitive delay is associated with diminished brain volume.[454,461–463]

We are just beginning to establish the pathologic evidence for why these deficits may occur. Presently, we demonstrate neuropathology correlation with neurodevelopmental disability in only the most severely affected newborns, and many infants without obvious neuroimaging abnormalities go on to manifest clinically detectable deficits. While some preterm infants have early diagnosis of motor or cognitive deficits with identified neurobehavioral or clinical risk factors, there are many who escape early detection, and manifest more subtle deficits much later in life.[437,464] Although predictive accuracy generally improves with factors that are associated with severe early impairment, our overall ability to identify clinical neurobehavioral risk factors, as well as neuroimaging correlates with long-term neuropathology lack sensitivity and specificity. In the extremely low birthweight infant, antenatal and clinical risk factors assessed over the 1st week of life did not improve predictability of death or neurodevelopmental impairment defined by the Bayley Scales of Infant Development II Mental Developmental Index scores at 18 to 24 months of age.[465] And this same assessment tool at 20 months has poor predictive value for cognitive function at school age.[466]

Brain development is a complex system, interacting with the environment through sensory systems that mature at differential rates. These interactions are multimodal, and the consequences of these interactions may be more web-like than linear. MacKendrick[467] has suggested the application of chaos theory to better understand the challenges in correlating early events with later outcomes. Early environmental challenges and short-term disability does not necessarily predict long-term outcome, and despite these early barriers, the brain may still compensate favorably. It has been suggested that this unpredictability is due in part to the compensatory effects of brain plasticity, and the ability of the human brain to favorably re-wire itself in the face of environmental insults.[466,468] An ecological perspective on human development is that long-term developmental outcomes will be determined by not only the biological and clinical factors, but also the complex integration of the human organism with his environment. Outcomes may be the summation of multiple pathways, where early interventions or treatments may be altered by compensatory developmental processes.[26,469]

The recommended care practices we discuss may be implemented concurrently or following multiple other practices and treatments, each with known or unknown potential for significant neurodevelopmental consequences. Although randomized clinical trials are still the best vehicle to measure true differences in short-term outcomes, longer-term outcomes, through the ameliorative process of brain plasticity, may become less detectable over time. This dynamics may make it difficult to detect measurable differences in isolated or more subtle changes in care practices, especially over longer periods of follow-up. The challenge of inadequately powered studies becomes especially daunting.

Advances in electrophysiology and neuro-imaging technology, including ultrasonography, event-related potentials, functional magnetic resonance imaging, diffusion tensor imaging and magnetic resonance spectroscopy[470–472] may increase our understanding of the correlations of structure and function and provide more sensitive and more specific structural evidence of the consequences of our treatments. Serial ultrasonography demonstrates diminished growth of the corpus callosum in the 23 to 33 weeks gestation preterm infant, with speculation that this finding may be a macroscopic correlate of diminished synaptic connectivity.[473] Diffusion tensor imaging has demonstrated measurable differences in cortical myelination for patients with controlled variation in early exogenous experience.[474]

This is an emerging field of study, and presently it is our working assumption that the optimal environment for the developing fetal brain is the human womb, and that the NICU environment of the preterm infant is a less favorable environment. Many negative environmental factors and environmentally related care practices have originated more from incidental expedience, rather than clinical or theoretical evidence.[475] Weighing potential risk against benefit, we need no additional justification to move towards an NICU environment that seeks to protect and support the developing newborn brain through gentler care practices and strategies to preserve sleep. It is our burden to ensure that our existing environment is, at the least, non-disruptive, and optimally, supportive for normal brain development. It is in this context that we provide these general recommendations.

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