THE UNIVERSITY OF KANSAS PREMIE NEUROSCIENCE RESEARCH PROGRAM:

Towards Universal Newborn Sensorimotor Screening and Habilitation

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Incidence and Cost

Nearly 450,000 babies are born prematurely into the world each year in the United States. Of this, approximately 25,000 babies are classified as "extremely premature" or micropremies (27 weeks gestational age [GA] or less). Simply stated, these babies are born too soon and are thrust into an environment using a partially developed nervous system, immature lungs and respiratory system, skin too thin and fragile to be handled or subjected to the dehydrating effects of ambient air, and emerging anatomy.

Concerning the financial impact on the family and society, medical care costs approach $750,000 for a single micropremie in the neonatal intensive care unit (NICU). The first month of care in the NICU for micropremies is an especially critical time period, with close involvement of a comprehensive team of medical care specialists. During the first month, these costs approach $65,000 per week. This translates to more than $15 billion annually to care for the micropremies until they reach term or 40 weeks gestational age. In the United States, the pooled costs among all preterm babies (micropremies + premies) is estimated at $200 billion annually and rising.

Another factor that deserves consideration is the fact that post term costs are much higher for premies during the first three years of life (infancy through preschool) compared to babies born at term. Many neurological problems are not discovered using traditional diagnostic tools until toddler, preschool, and elementary school years. It has been estimated that approximately 1:5 preterm babies will eventually manifest profound impairments. This translates to nearly 80,000 babies per year contributing to a pool of nearly a half a million pre-kindergarten children with severe-profound impairments (learning disability, pervasive developmental delay, sensory perception and integration disorders, sensorimotor dysfunction, cognitive impairments, literacy, language, and speech disorders). This estimate is limited to those children with salient, distinguishable disorders. The number of children with mild-moderate impairments is presumed to be much greater, perhaps an order of magnitude or more. The difficulty gauging the scope of impairment among young children is masked by developmental variability compounded with relatively insensitive diagnostic screening tools available to clinicians.

Obviously, the key is early identification. However, traditional wisdom has relied on a "wait" and "see" approach, due in large part to the lack of quantitative methods for assessing brain-behavior relations in NICU babies. This approach carries significant risk. The human brain undergoes dramatic changes during fetal development that extend well into the second decade of life. There are in fact a number of important critical periods that are dependent upon combinations of timing and experience to establish primary neural pathways for handling the barrage of sensory flow and eventual output to effector organs such as muscles and glands. There are also salient forms of stimulation that the baby needs to experience on a regular basis to form functional neural circuits. Certain classes of neurons also manifest endogenous (internally generated) forms of activity, the disruption of which can have serious ramifications on brain development. And finally, spontaneous or self-generated activities serve to trigger activity-dependent refinement of pathway formation and synaptic efficacy. Disruption of any of these processes can produce or contribute to significant neural delay. Fortunately there are potent mechanisms of neuroplasticity that afford the developing nervous system significant potential to recover or reorganize following periods of nutritive deficiency or insult to the developing brain.

The Goals and Objectives of the KU Newborn Neuroscience Program

During the past decade, a new approach and corresponding technology has been developed with the mechanisms of neuroplasticity in mind for premature infants at risk for brain insult, including: 1) objective, noninvasive assessment of functional neural status of centrally patterned orofacial and respiratory control, and 2) incorporation of neuroplasticity mechanisms of activity dependent change and multimodal coincident stimulation in a regimen for habilitating developing neural pathways in the premature infant (Barlow, Dusick, Finan, Coltart, Biswas, & Denne, 1999; Barlow, Dusick, Finan, Coltart, Biswas, & Flaherty, 2000; Barlow, Finan, Bradford, & Andreatta, 1993; Barlow, Finan, & Andreatta, 1997; Finan, 1998, Finan & Barlow, 1996, 1998). This second step provides neonatal specialists and developmental neurophysiologists with a set of intervention tools for inducing the developing nervous system to form preferred patterns of synaptic connectivity at a time in the baby's life when salient stimulation is crucial for pathway formation. The NICU experience, while effective in maintaining crucial life support functions of the fragile premie, nonetheless represents a significant period of sensory deprivation. With the face and nose taped and intubated, self-generated orofacial movements and autogenic stimulation of mechanoreceptors and nerve endings in skin and muscle that "register" the consequences of such patterned motor output is severely limited. It is hypothesized that this form of sensory deprivation, combined with pre- and perinatal trauma to the nervous system, contribute to the constellation of long-term of neurobehavioral, sensory aversion, and motor control deficits observed in early years of development. Appropriate oral experiences may be critical in the final weeks of gestation, and their interruption may impair fragile syntheses of central neural representations of functions (Bosma, 1972).

The ACTIFIER Technology

Combinations of funding from the National Institutes of Health, and corporate sponsorship (Gerber, Neuro Logic, RC Electronics) have been utilized during the past decade to fuel the science and technologic development of a new instrument and protocol capable of efficient, noninvasive sampling neuromotor activity, reflexes, and orofacial pattern generation in premies during sucking in the NICU. The research referenced in this report reflects the participation of an extensive team of scientists, medical specialists, and students at all levels of their training careers (Table 1).

TABLE 1. KU Newborn Neuroscience Program Research Team

Don S. Finan, PhD	University of South Carolina Speech Physiology/Neuroscience
Amitava Biswas, PhD	University of Texas El Paso Engineering/Neuroscience
Esther Thelen, PhD	Indiana University - Developmental Psychology
Rick Konopacki, MSEE	University of Wisconsin Servo Dynamics/Engineering
Anna Dusick, MD	Indiana University School of Medicine Neonatology/Dev. Pediatrics
Shirley Coltart, MSRN	Indiana University School of Medicine Neonatology
Preston Garraghty, PhD	Indiana University - Neural Plasticity
Carol Boliek, PhD	University of Arizona Developmental Physiologist
Kathy Weatherstone, MD*	KU Medical Center Neonatology and Perinatal Medicine

* In consultation for research team recruitment

Trigeminofacial Reflex Modulation. Indexing the excitability of brain pathways, including brain stem and cerebral cortex, during non-nutritive suck is achieved with a specially designed instrument known as an *actifier*. The actifier consists of a latex baglet (Gerber NUK neonate nipple), a pacifier shield instrumented with 8 Ag/AgCl surface electrodes (3 mm diameter) for sampling electrical activity from lip muscles, and an array of four servo linear motors that provide natural stimulation of mechanoreceptive fields roughly corresponding to the "hairy skin" quadrants of the upper and lower lip. Each linear motor is under precise computer control and can be operated under position or current feedback with adjustable tracking forces. The timing of the brief and gentle mechanical stimulation is indexed to the baby's own suck pattern so that the skin tap occurs at the same phase of suck generation. All components of the actifier that come into direct contact with the infant's mouth are gas sterilized (ethylene oxide) prior to each test session.

The relatively innocuous nature of this natural form of mechanical stimulation makes it possible to assess perioral reflex excitability in the context of a naturally occurring, patterned oromotor output in about 3 minutes. All biological signals, including EMG, suck pressure, and stimulus related signals are digitized by a personal computer in real-time at 100-microsecond dwell time for each channel.

All instrumentation, including signal conditioning, servo controllers, microprocessor, and support electronics for the actifier stimulator assembly can be wheeled cribside in the NICU for each test session. The mobility of this neonate orofacial laboratory station makes it possible to complete recordings cribside or adjacent to an isolette while maintaining the baby's connection to the physiologic monitors.

Non-nutritive Suck. The actifier also permits physiologic evaluation of suck status. These tests occur at cribside approximately 15 minutes before a feeding with the infant alert. Following a brief examination of neurologic state, the infant is positioned and settled comfortably in the arms of the attending physician or research nurse. A sterile baglet assembly (non-nutritive nipple) is coupled to the actifier and positioned in the baby's mouth. The data acquisition computer is triggered by the baby's spontaneous suck to sample all physiological signals related to the non-nutritive suck. This protocol is usually completed within 2 or 3 minutes. Data on the mechanics of the suck provide important information on the functional status of the orofacial system. Physicians and pediatric nurses use this information to make key decisions about feeding readiness.

Neonatal "Electricians." The role of early oromotor experience will be tested in future studies at the University of Kansas and affiliate neonatal intensive care units (Indiana University School of Medicine, University of Arizona) to assess the brain's plasticity in establishing new patterns of connections to facilitate oromotor development. The pattern of electrical activity and competitive interaction between adjacent nerve terminals are primary determinants of development and stability of synaptic connections (Garraghty, Kaas & Florence, 1994). In essence, **"neurons wire together, if they fire together"** (Sporns, 1994). One such technique used in motor physiology to recruit populations of neurons to fire synchronously is known as entrainment. Entrainment of rhythmic motor outputs is a powerful experimental approach for revealing moment-to-moment influences of mechanosensory inputs on motor control. Entrainment is defined as the synchronization of an endogenous oscillator (neural circuits that produce patterned output, i.e., walking, running, chewing, sucking) to an external pacemaker (Pavlidis, 1973; Glass & Mackey, 1988; Kriellaars, Brownstone, Noga & Jordan, 1994). In the current application, the external pacemaker is the actifier. The nipple of the actifier is coupled to a hydraulic motor that can be programmed to produce very rapid and periodic changes in the shape and size of the nipple. The human neonate suck is one such rhythmic motor pattern that has recently been demonstrated to be significantly influenced by an entraining actifier nipple (Finan, 1998). Term infants are known to match or entrain to the "pulsing" nipple of the actifier. The potential for re-wiring the human neonate brain using highly controlled and patterned mechanosensory input is enormous. Entrainment techniques will be offered to premies in the NICU setting with confirmed oromotor disturbances to induce synchronous firing of neural circuits in brain stem and suprabulbar structures. This is expected to induce terminal sprouting and the creation of new functional connections that underlie oromotor and respiratory patterning. Daily regimens of mechanical entrainment is predicted to improve the overall functional status of orofacial and respiratory systems that are involved in sucking, and quite possibly improve long term outcome for other sensorimotor skills involving these muscle systems (vocalization, speech, gesture).

Highlight of Experimental Findings on Premies and Term Infants

1. The actifier technology permits non-invasive assessment of functional brain-behavior relations and biomechanics during non-nutritive suck production in the premature infant.

2. Computerized measures of orofacial sensorimotor function can be obtained routinely and reliably in less than 5 minutes of actual computer-controlled recording time. Efficiency is paramount when

attempting to record sensorimotor behavior in neonates where vigilance is at a premium.

3. Non-nutritive suck dynamics change predictably as a function of maturation (age & experience) including longer, stronger, and more uniform suck burst patterns that appear correlated with changes in the neural integrity of trigeminal and facial cranial nerve systems.

4. The actifier reflex protocol permits objective indexing of the speed of neural transmission through brain stem and cortical pathways using highly controlled, innocuous mechanical stimulation delivered to the surface of the upper and lower lip during non-nutritive suck. As the neonate matures, the speed of neural transmission in the brain stem increases thereby improving the capacity for sensorimotor integration. Variants of this protocol can be used to determine functional participation by cortical circuits during suck, thus indirectly assessing the "health" of select cerebral pathways.

5. Oromotor, and recently respiratory entrainment appear to show great promise as tools for synchronously activating large populations of pathway specific neurons in order to reinforce the probability of desired patterns of motor output.

Future Directions

Research efforts will include an expanded research team and a set of experimental questions designed to map the dynamics of neural modulation between brain stem and cerebral systems in the premies during non-nutritive suck, nutritive suck, and patterned respiratory activity. Populations will include medically stable preterm infants as well as babies with suspected ventricular hemorrhage, respiratory distress syndrome, and genetic syndromes affecting brain function.

Concurrent experiments on the efficacy of entrainment therapy in the NICU will be conducted with systematic tests of modality type and multimodal entrainers applied to infants with known oromotor control problems. Parallel experiments in an animal model (fetal rat pup) will permit quantitative assessment of changes in brain connectivity at the level of synaptic arborization, efficiency, distribution, and typing in treated populations. The goal in these types of animal experiments is to identify the salient stimulation parameters that induce desired mechanisms of neuroplasticity in a developing brain.

Special efforts will be directed to develop a series of longitudinal outcome studies to identify links between early brain insult (hemorrhage and nutritive deficiency) and later appearing impairments (communication, cognitive, learning, and sensorimotor including speech, locomotion and manipulation).

Summary

Collaboration is essential for the type of research program described in the current report where the target application transcends the initial working idea from the engineering workbench to cribside in the neonatal intensive care unit. It is a team effort, involving the expertise of dozens of professionals including hardware and software engineers, mechanical design specialists, machinists, biomechanists, electrophysiologists, statisticians, pediatric nurses, developmental pediatricians, neonatalogists, undergraduate and graduate students, and post-doctoral research fellows. Research team building involves recruitment of talented individuals among several disciplines (departments) both within a university system, and frequently, establishing cooperative arrangements among two or more universities. I have found that what motivates such a diverse set of team members is the pursuit of knowledge and the altruism that drives us to solve a complex problem that degrades the human condition.

To gain access to clinical test sites, the principal investigator must convince the host site that the question under study is significant and bears direct relevance to patient care in their facility, with little or no risk to the test population. In the current report, we are interested in early detection and remediation of developmental or acquired neurological conditions in premature infants that are presumed to contribute to a constellation of developmental disorders that are manifest during toddler and preschool years. Thus far, the neonatal intensive care units have accommodated our research protocols with great enthusiasm. Medical directors of the NICU's and participating physicians have become strong advocates of the ACTIFIER technology and neurophysiological test protocols used with the premies under their care.

Biomedical research costs money, and principal investigators are responsible for generating grant applications to support innovative research programs. Without extramural support, research programs languish and progress is slow. The University of Kansas Premie Neurosciences Research Program represents the programmatic evolution of a research line into human neurologic disorders that began at Boys Town National Institute in the 1980's, moved on to Indiana University throughout the 1990's with concentration on pediatric sensorimotor neurophysiology and premie neurological monitoring in the neonatal intensive care unit, and now to the University of Kansas in the new millenium where we will accelerate the exploration of mechanisms of brain plasticity in newborns at-risk for brain injury. Funding has been provided by multiple sources including the National Institutes of Health (NIDCD, NICHD), and corporate sponsors (Gerber, Neuro Logic, RC Electronics). Additional funding sources are needed to expand the KU Premie Neurosciences Research Program to include multi-institutional participation by regional NICU centers in the United States. This will help to increase the size of the test populations, and improve statistical power in determining the most efficacious methods of brain monitoring and therapeutic stimulation in premies as sensorimotor systems proceed through critical periods of neural refinement.

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