# Patterns of Altered Neurobehavior in Preterm Infants within the Neonatal Intensive Care Unit

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**Objective** To investigate differences in neurobehavior between preterm infants at term and full-term infants, changes in neurobehavior between 34 weeks postmenstrual age (PMA) and term equivalent in the preterm infant, and the relationship of neurobehavior to perinatal exposures.

**Study design** In this prospective cohort study, 75 infants were tested at 34 weeks PMA and again at term using the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Infants underwent magnetic resonance imaging at term equivalent. Regression was used to investigate differences in the scale's domains of function across time and in relation to perinatal exposures.

**Results** At term equivalent, preterm infants exhibited altered behavior compared with full-term infants, with poorer orientation ($P < .001$), lower tolerance of handling ($P < .001$), lower self-regulation ($P < .001$), poorer reflexes ($P < .001$), more stress ($P < .001$), hypertonicity ($P < .001$), hypotonia ($P < .001$), and more excitability ($P = .007$). Preterm infants from 34 weeks PMA to term equivalent, demonstrated changes in motor functions with declining quality of movement ($P = .006$), increasing hypertonia ($P < .001$), decreasing hypotonia ($P = .001$), and changes in behavior with increasing arousal ($P < .001$), increasing excitability ($P < .001$), and decreasing lethargy ($P < .001$). Cerebral injury was associated with more excitability ($P = .002$). However, no associations were detected between any of the perinatal exposures and developmental change from 34 weeks PMA to term equivalent.

**Conclusion** Preterm infants have altered neurobehavior in a broad number of domains at term equivalent. Cerebral injury alters neurobehavior but does not appear to impair early neurobehavioral changes. Important neurobehavioral changes occur before term, and this provides an opportunity for interventions in the neonatal intensive care unit. *(J Pediatr 2013;162:470-6)*.

Neonatal intensive care units (NICUs) have undergone dramatic changes in practice since their inception in the 1960s.[1] With improved perinatal and neonatal care, the survival rate for preterm infants has increased substantially.[2] Although life-saving strategies have improved, preterm infants remain at increased risk for neurodevelopmental difficulties later in life, including cerebral palsy, motor coordination problems, attention deficit hyperactivity disorder, executive functioning disorders, and cognitive delays.[3-5] The risk of impairment increases with decreasing gestational age at birth.[6] Thus, extremely low birth weight infants are at the greatest risk for developmental problems; in a previous report, only 25% of these infants demonstrated normal development at age 5 years.[7] Therefore, the study of early development in those born at the most vulnerable gestational age is warranted to enable an improved understanding of what factors alter function and what interventions can optimize outcome.

Both cerebral injury and altered cerebral development can influence neurodevelopmental outcome in preterm infants. Cerebral injury is common in extremely preterm infants, with approximately 25% suffering intraventricular hemorrhage and 50%-70% displaying white matter abnormalities on magnetic resonance imaging (MRI).[8] Cerebral injury and/or alterations in typical cerebral development may influence neurobehavior in the final weeks and months of extrauterine life, along with longer-term neurodevelopmental outcomes. Although research on the changing brain structure of the preterm infant has been reported,[9,10] the progression of neurobehavior in the preterm infant before term has received less attention. Well-defined and rapid changes in development during the first year of life help identify infants who deviate from normal development; however, to our knowledge, changes in early neurobehavior before term have not yet been described.

Preterm infants in the NICU are exposed to medical interventions, such as mechanical ventilation, and are at-risk for numerous complications associated

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| EGA | Estimated gestational age |
| MRI | Magnetic resonance imaging |
| NEC | Necrotizing enterocolitis |
| NICU | Neonatal intensive care unit |
| NNNS | Neonatal Intensive Care Unit Network Neurobehavioral Scale |
| PDA | Patent ductus arteriosus |
| PMA | Postmenstrual age |

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Supported by the National Institute of Health (R01 HD057098), the Washington University Intellectual and Developmental Disabilities Research Center (NIH/NICHD P30 HD062171), and the Doris Duke Foundation, none of which were involved in the study design, data collection, interpretation of data, writing the report, or in the decision to submit the paper for publication. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2012.08.011

with preterm birth, including necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), retinopathy of prematurity, and sepsis. Despite the long-term developmental problems associated with prematurity and the potential influence of early medical factors in the NICU, the effects of different perinatal exposures on the progression of early neurobehavior have not been reported.

Methods for neurobehavioral evaluation of preterm infants have been developed.[11-13] Neurobehavioral testing is noninvasive and can be performed by health care professionals in the unit. One such neurobehavioral assessment is the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS).[11,14] Originally developed for use in high-risk infants, the NNNS has recently gained acceptance as a tool for use in preterm infants.[14,15] Use of the NNNS has demonstrated that cerebral injury negatively affects early neurobehavior, resulting in poorer attention and more nonoptimal reflexes.[14,16] In addition, the pattern of neurobehavior revealed by the NNNS—specifically, the presence of increased excitability, arousal, hypertonicity, and stress in conjunction with lower scores for quality of movement, orientation, and self regulation—has been shown to be predictive of adverse outcomes.[17] However, to our knowledge, use of the NNNS at 2 time points before term as a measure of neurobehavioral change has not yet been reported.

## Methods

This study was a prospective cohort design recruiting inborn admissions of preterm infants born at less than 30 weeks estimated gestational age (EGA) within the first 3 days of life between 2007 and 2010. Sample size calculations were conducted before enrollment. A sample size of 84 was needed to detect a medium effect with 80% power and $\alpha = 0.05$; thus, we planned to enroll 120 infants to account for attrition. We chose a medium effect, given that small differences in neurobehavior might be associated with lesser effects of the NICU environment or medical interventions, and large differences would not be expected during the short (6 weeks) period of development under study. The study was approved by the Human Research Protection Office.

Exclusion criteria included having a known congenital anomaly or being moribund with severe sepsis or respiratory failure in the first days of life. All infants whose parents provided informed consent were enrolled in the study and underwent neurobehavioral assessment, electroencephalography studies, and MRI at birth, 30 weeks postmenstrual age (PMA), 34 weeks PMA, and term equivalent (as medical status and interventions allowed). Information on medical interventions and health conditions associated with prematurity were obtained from the medical record. Data from an NNNS evaluation conducted at 34 weeks PMA and another NNNS evaluation conducted at term equivalent were used. Different tools for assessing neurobehavior were used at the earlier time points, because it was felt that infants born at 30 weeks PMA or earlier could not tolerate the comprehensive NNNS assessment. Earlier neurobehavioral testing at birth and 30 weeks PMA are not presented. The change in NNNS summary scores, calculated by subtracting the 34-week PMA NNNS score from the term equivalent NNNS score, was determined for each infant in the study.

### Cerebral Injury by MRI and Cranial Ultrasound

Infants underwent cranial ultrasound evaluations at least once within the first week of life and also at 1 month of life as part of routine clinical care. These data were used to identify the presence or absence of intraventricular hemorrhage and to classify the severity (grade I-IV). Each infant also underwent serial MRI, with a final scan performed at term equivalent. MRI was performed with a neonatal nurse present, under continuous cardiovascular monitoring, and without sedation. Conventional MRI images were used to describe cystic periventricular leukomalacia and cerebellar hemorrhage. Cerebral injury was dichotomized into present or absent, and was defined as the presence of one or more of the following: cerebellar hemorrhage, intraventricular hemorrhage grade III or IV, and cystic periventricular leukomalacia.

### Medical and Environmental Exposures

Information on other medical and environmental exposures was obtained from the medical record. Completed weeks of gestation at birth (ie, EGA) and Critical Risk Index for Babies scores were recorded. The number of days of intubation, use of oxygen after 36 weeks corrected age, and use of postnatal steroids were also documented, and any other complications associated with prematurity, including PDA, NEC, and sepsis, were noted.

### Outcome Measures

Infants underwent neurobehavioral testing with the NNNS within 1 week of 34 weeks PMA (ie, 33-35 weeks gestation) and then again at term equivalent (37-41 weeks gestation). All examinations were performed by a single trained and certified NNNS examiner blinded to the presence or absence of cerebral injury. Each examination was completed approximately 30 minutes before a scheduled feeding or hands-on care time. All evaluations were videotaped for reliability of scoring.

The 115 NNNS items were scored and entered into an SPSS syntax (SPSS Inc, Chicago, Illinois), which appropriately weighed each item and generated 13 summary scores: habituation, orientation, tolerance of handling, quality of movement, self-regulation, nonoptimal reflexes, stress signs, arousal, hypertonia, hypotonia, asymmetry, excitability, and lethargy. Each summary score ranged from 0 to 13. Higher summary scores indicate more of the function observed during the testing; lower scores, less of the function. Summary score values for a healthy full-term infant sample were used for comparison.[12] This comparison sample was comprised of 125 1-day-old infants born at full term to mothers aged 18-39 who were free of any condition that could affect perinatal health, had no evidence of brain injury, did not require intensive care, had no evidence of drug or alcohol exposure, and who were discharged with the mother by day 3 of life.