

Maternal and Child Health Research Program

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Final Report

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I. Introduction

Nature of the Research Problem

Despite impressive advances in neuroimaging techniques that visualize brain injury in fullterm and preterm infants, neuroimaging cannot replace the use of clinical skills to assess the rate and quality of an infant's functional development for the early diagnosis of neurodevelopmental disabilities (e.g. cerebral palsy, intellectual disability). Neuromaturation is the functional development of the central nervous system (CNS), a dynamic process that results from continuous interactions between the genome and first, the intrauterine, and then the extrauterine environment. The ability to measure early neuromaturation, along with an assessment of risk factors and neuroimaging studies, can improve prediction of neurodevelopmental outcomes for preterm infants in a neonatal intensive care unit (NICU). Better prediction of neurodevelopmental outcomes facilitates not only parent counseling (who have difficulty coping with uncertainty), but also more efficient allocation of limited comprehensive developmental follow-up and early intervention resources. Measures of CNS function prior to term have the potential to promote developmental support for NICU infants, alert NICU personnel to treatments that adversely influence preterm brain development, and help determine the most effective strategies for promoting recovery from brain injury.

B. Purpose, Scope and Methods of the Investigation

This prospective longitudinal study of over 300 preterm infants recruited from 2 NICUs evaluates the validity and predictive accuracy of specific, unique measures of preterm CNS function. Using serial examinations of tone, reflexes and responses while they are in the NICU, we quantified each infant's degree of abnormalities and degree and rate of neuromaturation. Infants had neurodevelopmental evaluations at term (i.e. near their due date) and 18 to 24 months later. The 3 specific aims were to: 1) establish norms in a sample with no evidence of brain injury, cerebral palsy or intellectual disability; 2) evaluate effects of a prenatal, perinatal and postnatal risk factor: intrauterine growth restriction (IUGR), intraventricular hemorrhage (IVH) & chronic lung disease (CLD); and 3) determine their ability to predict cognitive, motor and language outcomes at 1.5-2 years from term.

C. Nature of the Findings

In normal preterm infants, muscle tone, reflexes and responses emerged in a predictable pattern, with expected individual variability, whether neuromaturation was intrauterine or extrauterine. Preterm IUGR infants had significantly lower rates of neuromaturation in the NICU compared to preterm infants who were appropriate for gestational age (AGA). Although there was a tendency for infants with IVH or CLD to have lower rates of neuromaturation, differences were not statistically significant between infants with and without those risk factors. Prenatal and postnatal risk factors associated with inflammation and infection (e.g. maternal dental problems, infant sepsis), and pathways to preterm birth felt to be due to infection and inflammation (premature rupture of membranes) were significantly associated with lower rates of neuromaturation. Exciting preliminary analyses suggest a close relationship between our measures of preterm extrauterine neuromaturation and cognitive abilities at 1.5-2 years from term. Our unique measures capture the dynamic nature of development. They require expertise but no technology, and can be used wherever trained clinicians encounter preterm infants.

II. Review of the Literature

A. Preterm Birth and Its Complications

Dramatic improvements in survival of infants of all gestational ages (GA), increasing preterm birth rates, and no concomitant reduction in risks for neurodevelopmental disabilities have turned preterm birth into a major U.S. public health problem [27]. Although just 13% of U.S. births are preterm, 64-75% of infant deaths, 42-47% of children with cerebral palsy, 27% with intellectual disability, 37% with visual impairment, 23% with hearing impairment, and up to \$611 million in special education costs can be attributed to preterm birth [39, 1, 27]. A conservative estimate by the Institute of Medicine as to the economic burden associated with U.S. preterm births was \$26.2 billion in 2005, or \$51,600 per preterm infant over the costs for a fullterm infant [27].

Prematurity is not a single disease but a complex condition with multiple interrelated environmental, biological and genetic risk factors contributing to poorly understood pathophysiologic pathways leading to birth before 37 weeks gestation. Although prematurity is associated with many biological, environmental and even genetic factors, the strongest predictor is a prior preterm birth [48, 76, 27, 42, 49, 51, 71, 72, 70]. Maternal illness (e.g. chronic hypertension, periodontal disease) and pregnancy complications (e.g. preeclampsia, abruption placenta) often contribute to preterm delivery.

Pathways include spontaneous preterm labor (PTL, 50%), preterm spontaneous rupture of membranes (ROM, 30%) and preterm delivery for maternal or fetal indications (MFI, 20%)[1]. Many factors that contribute to preterm birth also contribute to preterm brain injury (especially those that are associated with infection and inflammation) [36, 38, 52, 72]. Multiple gene-environmental interactions are implicated in both preterm birth and neurodevelopmental outcomes [53, 48, 52, 49, 72].

The vulnerability of immature organ systems, and mechanisms that precipitate preterm birth can lead to complications of prematurity. The most feared complications are CNS injury and altered neuromaturation: for more than 50 years, preterm outcome studies have reported higher rates of cerebral palsy, intellectual disability, sensory impairments, academic difficulties and behavior problems in children born preterm as compared with those born at term [4, 27, 6]. Disability risks increase with decreasing gestational age, but even the larger late preterm infants born at 32-36 weeks gestation have a higher risk of disability than fullterm infants [18, 54, 57, 27, 62]. Infants born at the limit of viability (22 to 25 weeks gestation) have the highest risks of neurodevelopmental disability [61, 22, 27, 49]. The most frequent impairment in preterm children is cognitive, leading to intellectual disability or specific learning disabilities [61, 57, 27, 62]. Children born preterm who have no major disability are still at high risk for the milder deficits of executive, visuospatial, sensorimotor and fine motor function that adversely influence their school performance, peer relationships and self-esteem [24, 61, 27, 60].

B. Neonatal Assessments of CNS Function and Prediction of Neurodevelopmental Outcome

Much progress is being made in visualizing the preterm infant's brain, and recognizing patterns of structural CNS injury. Serial head ultrasounds are a valuable bedside tool for visualizing the brain of even the sickest preterm infant. Evidence of brain injury or altered brain structure seen on ultrasound include: hemorrhage (subependymal, intraventricular or intraparenchymal); ventriculomegaly (dilated ventricles); cysts or other evidence of white matter injury (WMI); and reduced size of the corpus callosum (compared to fullterm infants). Although each of these ultrasound findings is associated with adverse neurodevelopmental outcomes, they cannot diagnose neurodevelopmental disability [22, 23, 29, 58, 67]. In a 2007 study of infants with birthweight below 1000 g, 28-30% of infants with intraparenchymal hemorrhage or white matter injury were normal at 18 to 22 months, while 39% of children with normal head ultrasounds had neurodevelopmental impairment [29].

Increasingly sophisticated neonatal neuroimaging studies hold great promise for improving prediction of neurodevelopmental disabilities [56, 37, 81, 25, 55]. MRI studies at term have identified white matter injury - a strong predictor of cerebral palsy - in 18-21% of very preterm infants [81, 55]. Diffusion tensor magnetic resonance imaging (DTI) allows visualization of the white matter tracts within the brain, and abnormalities of these tracts are associated with cerebral palsy and severe gait abnormalities [25, 73]. Concerns about expense and human resource requirements (to move and keep an infant still for MRI or DTI), as well as insufficient data regarding sensitivities, specificities, and positive and negative predictive values, hinder their incorporation into standard neonatal intensive care [37].

Early diagnosis of neurodevelopmental disability still requires clinical assessments of CNS function (e.g. motor milestone achievement, acquisition of language, assessment of cognitive abilities) during infancy and early childhood [79]. Interest in assessments of CNS function in very young infants has led to the development of a number of neurodevelopmental and neurobehavioral methods of assessing CNS function in the fetus, preterm infant, fullterm neonate and young infant [15, 59, 2]. The Amiel-Tison Neonatal Assessment at Term (ATNAT), the Dubowitz Neurological Examination of the Fullterm Newborn, Prechtl's Assessment of General Movements (GM) and the neurodevelopmental examination used in this project all correlate well with neuroimaging evidence of preterm brain injury [77, 11, 28, 40, 65, 16, 66, 47, 41, 45, 50, 68, 69, 81, 2]. Most studies demonstrate the reassuring nature of normal neurodevelopmental assessments, with negative predictive values of 82 to 100% [2]. Abnormalities on these assessments are associated with higher risks of neurodevelopmental disability. Quantification of the number and severity of exam abnormalities increases risk of disability [11]. Most methods become more predictive in the months following term [11, 33, 34, 16, 47, 69]. With Prechtl's GM assessment, immature writhing movements are replaced by fidgety movements at 6 to 9 weeks after term; the presence and quality of fidgety movements at 3 to 5 months improve the sensitivity and specificity for predicting cerebral palsy [44, 45, 43]. Several studies suggest that GMs are better predictors than the Dubowitz assessments, but studies do not agree as to whether the ATNAT or GM assessment best predicts preterm outcomes [33, 34, 47, 69, 2, 43].

The preponderance of evidence confirms strong relationships between a number of methods that assess early CNS function and neurodevelopmental outcomes in both fullterm and preterm infants. These assessments provide different information than do neuroimaging studies. Prediction is improved when neonatal CNS functional measures are combined with neuroimaging evidence of brain injury [77, 11, 80, 16, 68, 69]. Infant assessments of CNS function require expertise, but not expensive technology [64].

Drawing on the work of many others, Allen and Capute developed a comprehensive neonatal neurodevelopmental examination to predict preterm neurodevelopmental outcomes [11, 2, 3]. It consists of items that assess posture; movement; muscle tone; deep tendon, pathological and primitive reflexes; sensory responses; and behavior. In a sample of high risk preterm infants, number and severity of abnormalities on examination at term improved prediction of cerebral palsy and cognitive impairment [11]. This initial focus on abnormalities shifted with our recognition that criteria for normal scores on many exam items changed with the infant's postmenstrual age (PMA, GA plus chronological age) [10, 9, 12, 5, 3]. To assess an infant's degree of neuromaturation, we derived a Maturity Score by adding together scores on the examination items that changed with PMA. By plotting an infant's Maturity Scores against the PMA at the time of her exam, we use an estimated line of best fit to describe *the individual preterm infant's degree and rate of extrauterine neuromaturation* at a standard (and arbitrary) PMA. When comparing groups of infants in pilot data for this study, lower Maturity Scores were associated with IUGR, IVH and CLD, but not multiple gestation [13, 5]. Although other researchers have followed the development of preterm infants, *no other method so successfully integrates the dynamic nature of development into their assessments of CNS function.*

III. Study Design and Methods

A. Study Design

This prospective longitudinal study (titled the PANDA study, for Preterm Assessment of Neurodevelopment and Achievement) followed a cohort of preterm infants recruited from two NICUs in Baltimore City, MD. Infants were examined with a comprehensive neurodevelopmental examination at several times during their NICU hospitalization. They were brought in from home by their parents, or were still in the hospital, for a similar examination at term (i.e. 40 weeks postmenstrual age, PMA=GA + chronological age). Pertinent medical information was collected from medical records during their hospitalization, and demographic and family information from interviewing their parents. Families were followed with a phone survey of their infant's health, development and resource utilization every 4 months. When the infants were 18-24 months from term, their families brought them in for an assessment of their motor, cognitive, and language abilities.

B. Population Studied

Preterm infants were recruited from the Johns Hopkins Hospital and Bayview Medical Center NICUs for this project. Both centers serve impoverished or immigrant families in Baltimore and sick high risk mothers transferred from cities and rural communities all over Maryland and neighboring states.

C. Sample Selection

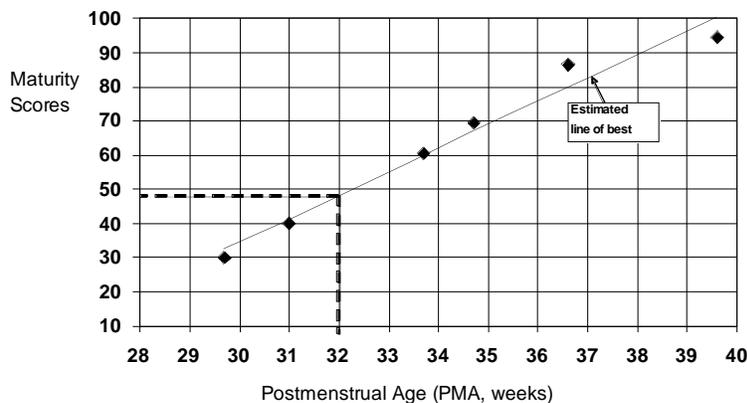
Preterm infants who were eligible for this study had BW below 1500 g or GA before 33 weeks, were hospitalized for at least 3 weeks, and had families who lived in Maryland. Families who knew they were moving out of the area generally declined or were excluded. Exclusion criteria included residence in another state and in very southern Maryland (added soon after starting recruitment, after talking with families who stated the distance to travel for follow-up exams was prohibitive). Congenital anomalies are risk factors for spontaneous preterm birth or may precipitate a decision to deliver preterm [51], so we included preterm infants with anomalies if the anomaly (or other medical condition, e.g. fracture) did not significantly interfere with our examinations. NICU staff determined whether an eligible infant was no longer critically ill and if they anticipated that the infant would be hospitalized for at least 3 weeks (for our weekly examinations). HIPAA requirements were introduced at the beginning of our study, and the initial required wording of consent forms was problematic for some families. The complexity of determining study inclusion made recruitment more difficult, and enrollment continued for 5 years to obtain a sample of 356 infants. For the most part, the racial and ethnic distribution reflects that of the 2 NICUs: 50% are African-American, 44% are Caucasian and 1.7% are Asian-American. Although we intended to target impoverished immigrant Hispanic families in Baltimore (and translated consent forms into Spanish), only 4% were Hispanic: recruitment was limited because of family fear of HIPAA disclosures and institutional requirements that parents give us their social security number before receiving financial incentives.

D. Instruments Used

Neonatal Neurodevelopmental Examination

Items in the comprehensive neonatal neurodevelopmental examination used in this project were developed by many researchers over the last century, and measure posture, movement, extremity flexor tone, axial (neck and trunk, through the body's axis) tone, deep tendon reflexes, pathological reflexes (Babinski), primitive reflexes scored in the manner of Capute [31, 30], postural reactions (head righting), sensory responses and behavior. The Abnormality Score is the sum of scores on items related to asymmetry, extensor tone, oromotor dysfunction, and abnormal posture, movement and behavior. The Maturity Score is the sum of scores on items that change with neuromaturation. Each infant's neonatal examination was scored as to degree of abnormality (Abnormality Score) and degree of neuromaturation (Maturity Score). For each infant, Maturity Scores were plotted against postmenstrual age (PMA) at the time of each exam, and computer software (SPSS) estimates a line of best fit (Figure 1). From this line, 2 indicators of neuromaturation are derived: 1) the slope of the line indicates rate of extrauterine neuromaturation in the NICU (Individual Maturity Slope), and 2) a y-intercept of the line gives a score for degree of neuromaturation (Predicted Maturity Score at a predetermined PMA, derived for each infant whether or not he was examined at that PMA). We arbitrarily chose a PMA of 32 weeks based on the tremendous individual variation we have observed at 32 to 34 weeks PMA as to whether the preterm infant breathes consistently on his own without caffeine, coordinates nipple and swallowing with breathing, and maintains his body temperature bundled in a bassinet. Figure 1 is an example of one infant's *Actual* Maturity Scores plotted by PMA: she was born at 28 5/7 weeks gestation and examined 6 times, with the last exam just days before term. The slope of her line of best fit is 6.9 (a value only meaningful when compared to other infants). The infant was not examined at 32 weeks PMA, but her Predicted Maturity Score at 32 weeks PMA is 49 (as demonstrated by the dotted lines).

Figure 1. Maturity Scores for an infant born at 28 5/7 weeks gestation.



In our pilot data, Maturity Scores plateaued at about 37 to 38 weeks PMA, so we added a number of exam items from that ATNAT to better capture degree of neuromaturation at and just after term [17, 50]

Outcome Evaluation Measures

Outcome evaluations at 18 to 24 months from term utilized the Bayley Scales of Infant Development-2nd edition, the Preschool Language Scale-4th edition (PLS), a neurological examination and Palisano's Gross Motor Function Scale (GMFS) [16]. The Bayley Mental, Psychomotor and Behavior Scales and the PLS are standardized instruments that have been used in many studies of preterm infants. The neurological examination provides a clinical diagnosis as to whether or not the child has cerebral palsy (CP). The GMFS scores reflect severity of a child's motor disability for age on a scale of 1 (normal function) to 5 (unable to move head and trunk against gravity). The major outcome variables are: Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI), PLS Score, CP Yes/No, and GMFS. We are continuing to obtain and enter outcomes data.

E. Statistical Techniques Employed

Data were collected from mother and infant's electronic and paper medical records, examinations of the infants, interviews with a parent (usually the mother), and clinical evaluation of the infant at 18 to 24 months from term. Data were entered into 2 databases (one for each infant's neonatal neurodevelopmental examinations, and the main study database with all other data). In the exam database, the Maturity and Abnormality Scores were derived, and these data were entered into the study's main database. For each infant, SPSS was used to graph Maturity Scores against PMA, and estimate a line of best fit using the Curve Estimation function. The slope (Individual Maturity Slope) and Predicted Maturity Score at 32 months were derived from the line of best fit, and entered into the study database for data analysis. Student's t-test, Chi-square test and ANOVA were used to analyze variables. Linear and logistic multiple regression models are used to control for confounding variables.

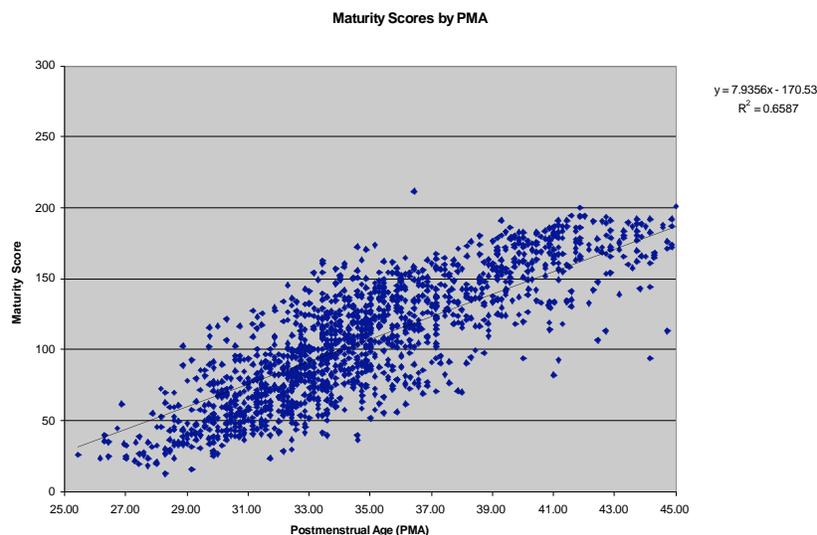
IV. Detailed Findings

During the first years of this project, we performed detailed data analyses on our pilot data from serial neonatal neurodevelopmental examinations in over 500 infants examined in the 1990s at Johns Hopkins Hospital. Experience with analyzing these data will guide us in analyzing the complex PANDA data, which we collected prospectively on preterm infants born 2002 to 2006. Over 900 preterm infants were screened, and the PANDA study was discussed with parents of over 500 infants from 2 NICUs. Our recruitment of approximately 400 infants was hindered by 31 refusals, families with plans to move out of state, and infants discharged or transferred within 3 weeks of birth. Of 356 enrolled infants, 20 died: 11 during their initial hospitalization and 9 after discharge home or transfer to a chronic care facility. Table 1 lists maternal, demographic and infant characteristics for the 356 infants enrolled in the PANDA study.

Table 1. Characteristics of the Study Sample of Preterm Infants (mean \pm standard deviation or %)

Birthweight	1168 \pm 420 g	Multiple gestation	21%	IUGR	17%
Gestational age	28.6 \pm 2.7 wks	Maternal diabetes	6%	Narcotics in urine: Mom	14%
Maternal age	27 \pm 7 yrs	Chronic hypertension	14%	Narcotics in urine: Infant	6%
Did not graduate HS	18%	Preeclampsia	22%	DR ventilation	60%
Oxygen duration	16.5 \pm 22 days	Placental abruption	9%	DR chest compressions	6%
Ventilation duration	14 \pm 24 days	Placenta previa	2%	Received surfactant	27%
Apgar \leq 3 @ 1 min	25%	Chorioamnionitis	20%	Chronic lung disease	41%
Apgar \leq 3 @ 5 min	4%	Oligohydramnios	14%	Necrotizing enterocolitis	13%
Maximum bilirubin	8 \pm 3 mg/dL	Preterm ROM	33%	Sepsis (+ culture)	18%
No. of exams	4.1 \pm 1.2	Abnormal FHR	24%	Retinopathy (ROP)	18%
PMA at first exam	30.1 \pm 2.6 wks	Fetal compromise	4%	Neonatal seizures	4%
PMA at last exam	40.3 \pm 4.0 wks	Antenatal steroids	89%	Congenital anomalies	7%

Figure 2. Scatterplot of Maturity Scores Plotted Against PMA for the 1st 200 Infants

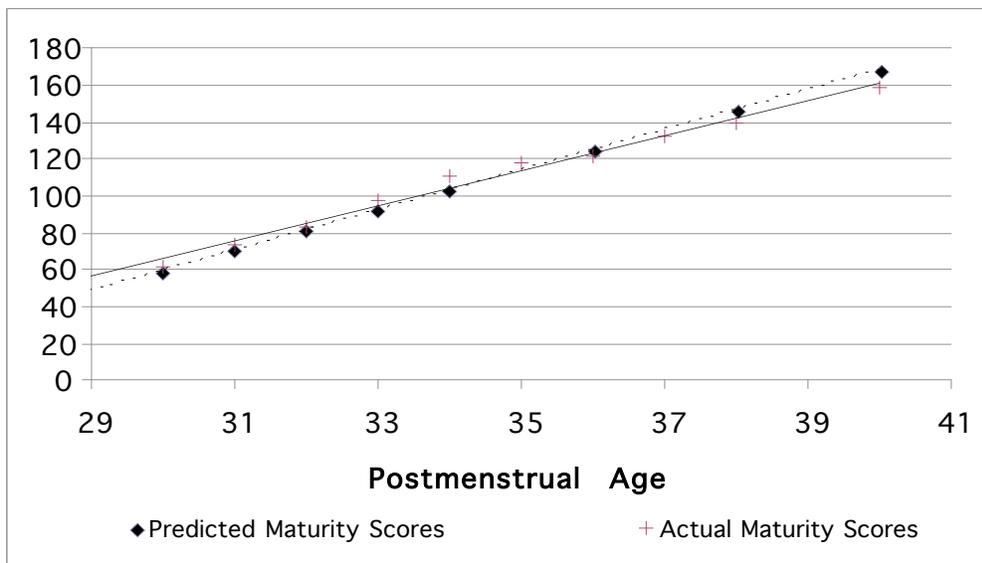


Over 1500 examinations were performed, with an average of 4.1 per infant and a range of 0 to 8. All examiners were experienced in caring for critically ill NICU infants, and performed exams only if NICU staff indicated an infant was stable (4 exams were stopped because the infant could not tolerate it). Some enrolled infants were critically ill for so long that only 1 or no examinations were performed before 44 weeks PMA. Nonetheless, 3 or more exams were completed on 312 (87%) of study infants. The initial

examination was generally performed at 29 to 30 weeks PMA (or at 7 days from birth for infants born after 29 weeks GA). Maturity Scores increased progressively, from 27 to 45 weeks PMA (Figure 2).

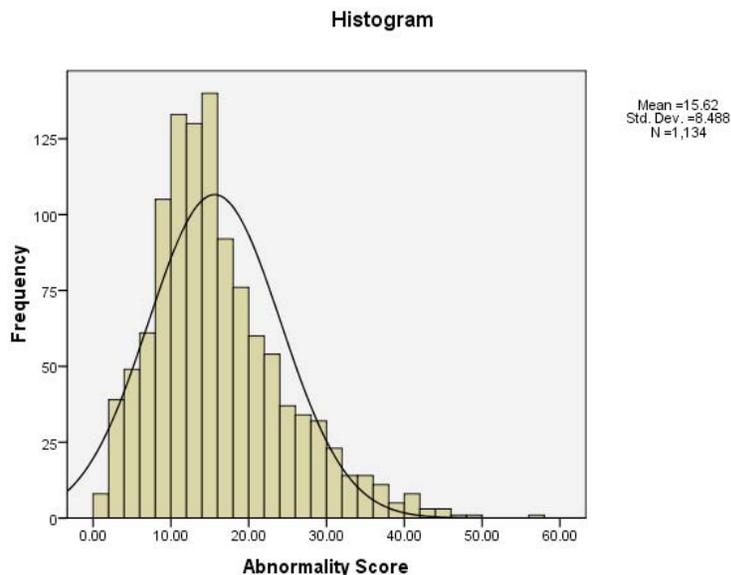
Figure 3 shows a close relationship between mean Actual Maturity Scores and mean Predicted Maturity Score values (from each infant's line of best fit) at 30, 31, 32, 33, 34, 36, 38 and 40 weeks PMA, for the total sample of preterm infants. The trendlines for actual and predicted scores are similar.

Figure 3. Means and Trendlines for Actual and Predicted Maturity Scores for Total Sample



To a much lesser extent, Abnormality Scores tended to increase with PMA (correlation coefficient 0.5), especially for exams before 32 weeks PMA. Figure 4 is a histogram of the distribution of Abnormality Scores for exams performed after 32 weeks PMA in the total sample. Abnormality scores range from 0 to 56, with a mean of $15.6 \pm SD 8.5$, median and mode of 14, skew towards 0 and a long tail to the right.

Figure 4. Distribution of Abnormality Scores in Preterm Infants Examined After 32 weeks PMA.

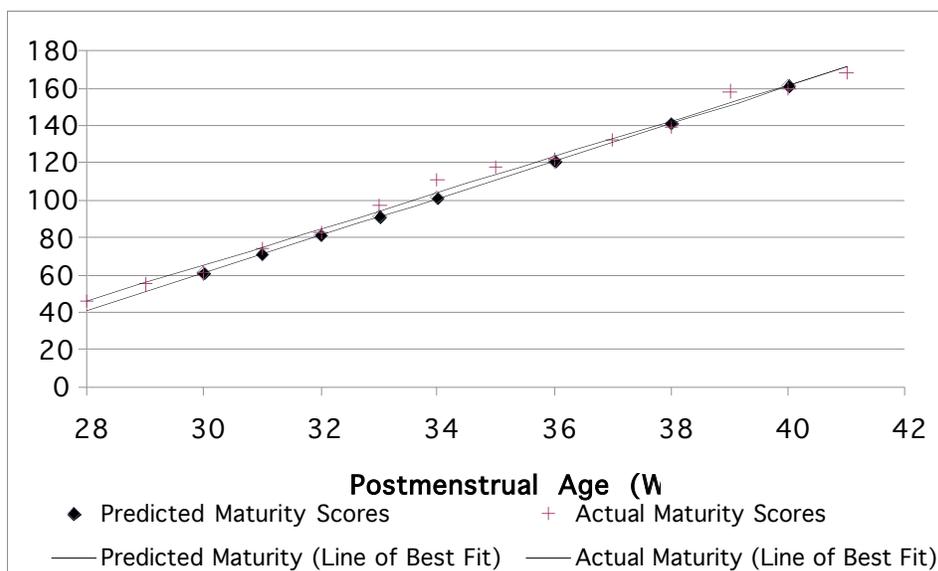


Specific Aim #1. To establish norms in a sample with no evidence of brain injury, cerebral palsy or intellectual disability

In our pilot data, Maturity Scores for 90 low risk preterm infants increased linearly with PMA (96% had correlation coefficients > 0.8). Predicted Maturity Score values corresponded well with Actual Maturity Scores at 32 weeks PMA, and extrauterine neuromaturation proceeded at the same rate as intrauterine neuromaturation. Preliminary analysis of PANDA study data allowed us to select 46 normal

preterm infants who had no brain injury *and* normal cognitive (MDI>80) and motor (PDI>70) abilities at 18 to 24 months. Figure 4 shows mean Actual and Predicted Maturity Scores as they increase linearly with PMA, with nearly identical data points and trend lines for normal preterm infants.

Figure 5. Mean Actual and Predicted Maturity Scores in 46 Normal Preterm Infants



In this small sample of 46 normal preterm infants, females had higher mean Predicted Maturity Scores at 32 weeks PMA, and there were no significant racial differences. In the total sample of 356 infants (Table 2), there were no gender differences but a tendency for nonwhite preterm infants to have higher mean Predicted Maturity Scores at 32 weeks PMA (p=0.06).

Specific Aim #2. To evaluate effects of a prenatal, perinatal and postnatal risk factor: IUGR, IVH & CLD

Lower Maturity Scores were associated with IUGR, IVH and CLD in our pilot data: all 3 had lower mean Predicted Maturity Scores at 32 weeks PMA, those with IVH or CLD had lower mean Individual Maturity Slope values, and CLD was the most consistent independent predictor of low Individual Maturity Slope values [5]. In more extensive analyses of pilot study growth and neuromaturation data, with multiple linear regression models, CLD was supplanted by early weight gain, sepsis and extreme IUGR variables as stronger independent predictors of low Individual Maturity Slope values. In the PANDA data (Table 2), mean Predicted Maturity Scores at 32 weeks PMA values were significantly lower in IUGR infants (p<0.05), with a tendency (p=0.06) toward lower mean Predicted Maturity Score at 32 weeks PMA values with CLD. There were no significant differences for IVH.

Table 2. Comparison of Rate and Degree of Neuromaturation for Risk Factors (Student’s t-test)

Factor	Rate of Neuromaturation: Mean Individual Maturity Slope Values			Degree of Neuromaturation: Mean Predicted Maturity Score at 32 wks PMA Values		
	Present	Absent	Significance	Present	Absent	Significance
Nonwhite race	10.6 ± 5.6	10.5 ± 6.9	ns	82 ± 36	76 ± 26	p= 0.06
Gender-Male	10.6 ± 6.5	10.6 ± 5.4	ns	80 ± 24	79 ± 28	ns
GA< 28 wks	9.5 ± 7.1	10.6 ± 7.9	ns	78 ± 26	83 ± 38	ns
BW< 1000 g	9.7 ± 3.6	11.1 ± 7.3	p< 0.05	76 ± 21	82 ± 29	p< 0.05
IUGR	10.7 ± 10.7	9.9 ± 8.0	ns	71 ± 23	83 ± 35	p< 0.02
IVH	9.5 ± 3.9	10.6 ± 4.4	ns	80 ± 21	80 ± 22	ns
O2 ≥ 28 wks	11.3 ± 7.1	10.5 ± 4.7	ns	80 ± 28	80 ± 24	ns
CLD	9.5 ± 4.2	10.4 ± 10.1	ns	76 ± 23	85 ± 42	p= 0.06

However, concerns about preterm brain injury have shifted over the last 5 years from IVH to evidence of white matter injury (WMI) [22, 29, 58]. In a smaller PANDA sample (n=148), WMI was associated with chorioamnionitis and funisitis (pathology evidence of infection of placental membranes and umbilical cord, respectively), infant sepsis, necrotizing enterocolitis (NEC) and retinopathy of prematurity (ROP). Lower mean Individual Maturity Slope values were seen with WMI (8.3 vs. 10.8, p<0.01), maternal dental problems during pregnancy (4.1 vs. 7.1, p<0.01), sepsis (with positive blood

cultures, 8.4 vs. 10.6, $p=0.02$), CLD (9.4 vs. 10.8, $p<0.05$), and ROP (8.3 vs. 10.4, $p<0.05$). Using linear regression models to control for confounders, WMI ($p<0.05$) and maternal dental problems ($p=0.001$) were the most consistent independent predictors of lower Individual Maturity Slope values.

In another exploration of maternal and prenatal factors and rate of preterm neuromaturation in 268 PANDA subjects, factors associated with pathway to preterm birth (Figure 5) included multiple gestation, IUGR, maternal illicit drug use, maternal diabetes, preeclampsia, chronic hypertension, fetal heart rate (FHR) abnormalities and absent end diastolic flow (EDF) on prenatal ultrasound (a sign of severe fetal compromise). Mean Individual Maturity Slope values were higher ($p<0.01$) in infants born after spontaneous preterm labor than in those born preterm after ROM or MFI.

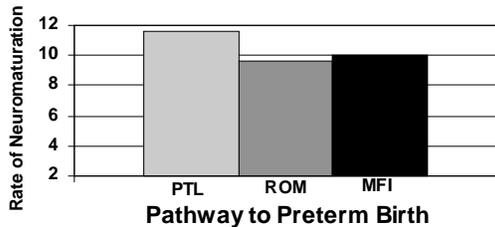


Figure 6. Mean Individual Maturity Slope Values by Pathway to Preterm Birth: Spontaneous Onset of Preterm Labor (PTL), Preterm Spontaneous Rupture of Membranes (ROM), and Preterm Delivery for Maternal or Fetal Indications (MFI)

Specific Aim #3. To determine the ability of our measures of early CNS function to predict cognitive, motor and language outcomes at 1.5-2 years from term

Although outcome data collection is continuing, preliminary data analyses are presented in Table 3 for Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI), Cerebral Palsy (CP) and Preschool Language Scale (PLS) Score. Preterm infants with MDI<70, PLS score<70 or a diagnosis of CP had lower mean Individual Maturity Slope values. There were no significant differences with PDI.

Table 3. Comparison of Rate and Degree of Neuromaturation by 18-24 Month Outcomes*

Outcome	Rate of Neuromaturation (Slope)			Degree of Neuromaturation: MS at 32 wks PMA		
	+	-	Significance	+	-	Significance
MDI<70	8.4 ± 2.9	10.4 ± 4.7	$p<0.05$	85 ± 22	79 ± 27	ns
PDI <70	9.4 ± 3.5	10.3 ± 4.7	ns	79 ± 27	81 ± 26	ns
CP	3.9 ± 3.6	10.1 ± 3.8	$p<0.01$	94 ± 16	81 ± 24	ns
PLS<70	7.1 ± 4.5	10.0 ± 4.4	$p=0.03$	81 ± 26	88 ± 15	ns

V. Discussion and Interpretation of Findings

A. Conclusions to be Drawn from Findings

We are encouraged with the reliability of Maturity Scores in measuring rate and degree of neuromaturation. Our efforts to analyze the neurodevelopmental exam findings in NICU infants born preterm in the 1980s led to the creation of our Abnormality and Maturity Scores [10, 9, 11, 12]. With funding from this project, we analyzed pilot data on over 500 preterm NICU infants born in the 1990s [13, 5, 14]. Maturity Scores increased linearly in low risk preterm infants, but tended to plateau just before term. We therefore added a number of exam items from the ATNAT [21, 17, 50] and several derived from our experience. In preterm infants with normal neurodevelopmental outcomes in the PANDA study, Maturity Scores increased linearly from 27 to 45 weeks PMA. Data points and trendlines for mean Actual and Predicted Maturity Scores between 30 and 40 weeks PMA virtually superimpose on one another. These data validate our methods of assessing rate and degree of preterm neuromaturation. Furthermore, they provide further evidence for Saint-Anne Dargassies’ assertion that preterm development proceeds in an orderly manner, whether in an intrauterine or extrauterine environment, according to age (GA or PMA) [74].

Strong correlations between cognitive abilities, language abilities, cerebral palsy and rate of neuromaturation suggest that these measures of preterm neuromaturation used in this project will provide important information for predicting preterm neurodevelopmental outcomes and providing insight into both causes injury to the developing brain and how it recovers from injury. Our preliminary analyses confirm that our measures of early CNS function provide information different from that provided by

neuroimaging studies (e.g. IVH, WMI), and can therefore enhance prediction if used in combination with neuroimaging. The associations between lower rates of neuromaturation and both preterm rupture of membranes and preterm delivery for maternal or fetal indications suggest that factors that lead to these 2 pathways to preterm birth may also injure the developing fetus's brain. Within the PANDA dataset, we need to further explore relationships between our measures of early CNS function and a number of demographic (race, gender, socioeconomic status), prenatal (IUGR, maternal dental problems, maternal illness), perinatal (pathways to preterm birth, resuscitation at delivery) and neonatal (CLD, sepsis, WMI, nutrition and growth) variables before drawing any firm conclusions. Nonetheless, the relationships between maternal and infant risk factors associated with infection and/or inflammation, brain injury and our measures of preterm neuromaturation provide further evidence that inflammation adversely influences both structure and function of the developing CNS.

B. Explanation of Study Limitations

The major concern with all outcome studies is related to the generalizability of these results to larger populations of preterm infants. This project encountered the usual challenges: 1) recruitment of all eligible infants, 2) performing assessments in a timely manner, 3) tracking families and 4) getting families to bring their children in for outcome evaluations. We encountered problems with all, but remained committed to enrolling high risk infants and families. Sections III.B and C above discuss recruitment concerns. After enrollment began, our institutional review board (IRB) prohibited enrollment of foster children in clinical research studies. It was very difficult to predict which infants would go into foster care (no decision is made until NICU discharge), or which would be physiologically stable and hospitalized for at least 3 weeks to allow serial examinations. Many infants were either too critically ill for examinations or were transferred to community hospitals before we could perform the planned 3-5 exams before 44 weeks PMA. (PI MCA obtained necessary medical staff privileges at 2 hospitals for exams on study infants). Despite these difficulties, we were able to perform at least 3 exams on 312 (85%) of study infants. Our efforts to track infants for outcome evaluations have been hampered by foster care placement, custody disputes and families who moved out of state (we traveled to Florida, California and Connecticut). We obtained additional funding to continue tracking and outcome evaluation efforts.

C. Comparison with Findings of Other Studies

The developmental literature consistently describes the different stages of development and how to assess them, but no other neonatal assessment method captures the dynamic aspects of development [5, 2, 3]. The progressively linear increase in Maturity Scores with PMA, as demonstrated in this project, is not only unique but confirms the central tenets of neurodevelopment. Further exploration of the PANDA data may provide insight into some of the fundamental aspects of neuromaturation. That gender or race may influence preterm neuromaturation is not surprising, as we and others have described their influence on infant milestone attainment [32, 8].

Exploration of relationships between rate and degree of preterm neuromaturation, medical illness and risk factors provides some insight into what influences brain development, injury and recovery from injury. There is good evidence, reviewed by Amiel-Tison, that acceleration of fetal maturation and earlier birth can be triggered by placental insufficiency as a fetal adaptation to stress [19, 20]. She has found that IUGR infants and infants from multiple gestations have an advanced degree of neuromaturation at birth, but she primarily examined infants born after 33 to 34 weeks gestation. Our preterm IUGR infants tended to have earlier, more severe IUGR, a high incidence of gastrointestinal problems in the NICU, and low Maturity Scores (lower than preterm appropriate for gestational age infants) [26, 14, 5]. The association between lower Maturity Scores with lower cognitive and language scores and cerebral palsy suggests that the adaptive mechanisms of placental insufficiency that accelerate neuromaturation are not yet present, are ineffective or are overwhelmed in these infants. It is reasonable to assume, then, that preterm delivery rescued these infants from further injury to the CNS, GI and other systems and may well have prevented fetal death *in utero*. Preterm delivery in this case is not preventable, and is *even advisable*.

Even if their neuroimaging studies are normal, preterm infants with significant neonatal illness (e.g. CLD, sepsis, NEC, ROP) have an increased risk of cognitive impairment and school difficulties [63, 4, 75, 78, 7]. Neonatal sepsis, CLD, NEC and ROP are all associated with inflammation or infection. Maternal risk factors for infection or inflammation include maternal urinary tract infections, dental problems (specifically, periodontal disease), and bacterial vaginosis, as well as infection or inflammation of the placenta or umbilical cord (chorioamnionitis, funisitis). These have all been implicated as causes or contributors to preterm birth and/or brain injury [38, 52, 71, 72, 70]. Our PANDA findings are consistent

with this literature: WMI was associated with chorioamnionitis, funisitis, neonatal sepsis, CLD, NEC and ROP; and lower rates of neuromaturation were associated with WMI, maternal dental problems during pregnancy, neonatal sepsis, ROP and CLD. Multiple linear regression models found WMI and maternal dental problems to be the most consistent independent predictors of low rates of neuromaturation. To our knowledge, maternal periodontal disease has only been associated with preterm birth, not injury to the preterm brain [71, 70].

D. Possible Application of Findings to Actual MCH Delivery

In conjunction with neuroimaging studies and assessment of biological and environmental risk factors, measures of early CNS function can optimize preterm outcomes by maximizing utilization of early intervention and comprehensive developmental follow-up resources, by providing insight into how the neonatal brain is injured and how it recovers from injury, and by facilitating clinical trials of NICU intervention strategies.

E. Policy Implications

Advances in clinical medicine do not always require the highest technology and most expensive resource utilization. In the 1950s, Virginia Apgar developed the Apgar score to focus attention on the newborn infant in the delivery room. This advance spurred research that led to marked improvements in neonatal resuscitation and survival. Advocating for the use of clinical tools to focus attention on under-recognized concerns requires dissemination of information and training, but not expensive technology. NIH funding for neonatal neuroimaging studies has focused a lot of attention on neonatal brain injury. Our measures of preterm neuromaturation promote awareness of preterm neuromaturation in the NICU, and facilitate the development of strategies that support development, minimize adverse interventions and promote recovery from brain injury. They can be used, in conjunction with neuroimaging studies and assessments of biological and environmental risk factors, for more efficient and effective allocation of comprehensive follow-up and early intervention resources and anticipation of future educational needs. Until effective strategies for preventing preterm birth can be developed, the greatest need is to optimize preterm outcomes.

F. Suggestions for Further Research

Using PANDA results and factor analysis of PANDA data, we will further refine our neonatal neurodevelopmental examination and reduce it to its key elements to reduce examination time. We have been continuing with data collection and entry of PANDA study infants' extrauterine growth and nutrition data. There is much controversy over what optimal extrauterine growth is, and what nutrition should be provided [46, 35]. Analysis of nutrition, extrauterine growth trajectories and rate of neuromaturation may provide further insights in to this complex question. We will evaluate the accuracy of Abnormality Scores, Individual Maturity Slopes, and Predicted Maturity Scores at 32 weeks PMA (both individually and in combination with the others) in predicting language, cognitive, motor and behavioral outcomes. Our clinical measures of early CNS function may be even more powerful in predicting neurodevelopmental outcomes when combined with serial head ultrasound evidence of brain injury.

VI. List of Products

Peer Reviewed Publications:

- 1) Allen MC: Assessment of gestational age and neuromaturation. MRDDRR 11: 21-33, 2005
- 2) Allen MC, Aucott S, Cristofalo EA, Alexander GR, Donohue PK: Extrauterine Neuromaturation of Low Risk Preterm Infants. In revision for Pediatric Research.

Chapters:

Allen MC, Donohue PK: Neuromaturation of multiples. In Blickstein I and Keith L (eds): Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome, 2nd edition, Taylor & Francis Group, New York, 2005.

Master Dissertation:

- 1) Simran K. Sabherwal, "Implications of maternal psychiatric symptomatology for preterm infant development." Thesis advisor: Pamela K. Donohue, ScD. For degree of Master of Health Science in Epidemiology, Bloomberg School of Public Health, Baltimore, MD.

2) Elizabeth A. Cristofalo, M.D., "Birth Weight, Early Weight Gain and Sepsis Predict Neuromaturation in Very Low Birthweight Infants." Thesis advisor: Pamela K. Donohue, ScD. For degree of Masters of Public Health, Bloomberg School of Public Health, Baltimore, MD.

Presentations at National and International Meetings:

1) Cristofalo E, Donohue PK, Alexander GR, Allen MC: Delayed neuromaturation in preterm NICU infants: Chronic lung disease, steroids and poor growth. *Pediatric Research* 53:441A, 2003. Presented at PAS platform session at PAS annual meeting, May, 2003.

2) Allen MC, Cristofalo EA, Aucott SW, Alexander GR, Donohue PK: Effect of intrauterine growth restriction on rate of preterm neuromaturation. *Pediatric Research* 55: 414A, 2004. Poster presented at PAS annual meeting, May, 2004.

3) Cristofalo EA, Donohue PK, Allen MC: Sepsis and early weight gain predict rate of neuromaturation in very low birth weight infants. *Pediatric Research* 2005. Poster presented at PAS annual meeting, May 2005.

4) Allen MC, Cristofalo E, Aucott S, Donohue PK: The relationship between neuromaturation prior to term and later motor abilities. *PAS* 57:1619, 2005 and *Neuropediatrics* 26:S74, 2006. Paper presented at the 5th Graz Symposium on Developmental Neurology, Graz, Austria, May 2005. Poster presented at PAS annual meeting May 2005 and the 10th International Child Neurology Congress in Montreal June 2006.

5) Allen MC, Cristofalo E, Aucott S, Alexander G, Jeffrey-Kwanisai, Donohue PK: Inflammation, white matter injury and early neuromaturation in preterm infants. E-PAS2007:617755.8 Presented at the PAS Annual Meeting May 2007, and poster presentation at the Child Neurology Society Annual Meeting October 2007.

6) Sabherwal SK, Donohue PK, Allen MC: Implications of maternal psychiatric symptomatology for preterm infant development. Paper presented at 13th Annual Maternal and Child Health Epidemiology Conference, December 2007.

7) Allen MC, Cristofalo E, Aucott S, Jeffrey-Kwanisai, Donohue PK: Relationships between pathways to preterm birth, pregnancy complications and preterm neuromaturation. Poster presented at PAS Annual Meeting May 2008.

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