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Alterations in Neurobehavior at Term Reflect Differing Perinatal Exposures in Very Preterm Infants

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ABSTRACT

OBJECTIVES. Preterm infants have higher rates of cognitive and behavioral difficulties at school age than their term-born peers. We hypothesized that neurobehavior at term would be different in very preterm infants compared with term infants and that perinatal exposures would be associated with these alterations in neurobehavior.

PATIENTS AND METHODS. Two standardized neurobehavioral evaluations were completed on 207 infants at term equivalent, including 168 very preterm infants (<1250 g or <30 weeks' gestation) and 39 term control infants. The assessments used were the Neonatal Intensive Care Unit Network Neurobehavioral Scale and the revised Hammersmith Neonatal Neurologic Examination. The relationship of perinatal variables to preterm infant neurobehavioral scores for both evaluations was examined.

RESULTS. Compared with term-born infants, preterm infant neurobehavior was significantly altered for the Hammersmith Neonatal Neurologic Examination total score and all of the subtotals. Similarly, preterm infants displayed altered neurobehavior for the majority of the Neonatal Intensive Care Unit Network Neurobehavioral Scale summary scores. Complete perinatal data were available for 157 of 168 very preterm infants. The perinatal variables most strongly associated with altered preterm infant neurobehavior on multivariate regression analysis included the total number of days of assisted ventilation, intraventricular hemorrhage, and necrotizing enterocolitis. Positive perinatal influences on neurobehavioral performance at term on multivariate analysis included maternal antenatal steroids, female gender, and infants receiving breast milk at discharge home.

CONCLUSIONS. Preterm infants at term equivalent showed alterations in motor behavior and higher cortically integrated functions. The pattern of abnormality in neurobehavior differed in relation to perinatal exposures. Neurobehavioral examination at term equivalent age is useful in evaluating the impact of neonatal intensive care.

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Key Words
preterm infant, very low birth weight, newborn infant, neurologic examination, child development, perinatal risk factors

Abbreviations
PMA—postmenstrual age
GA—gestational age
IUGR—intrauterine growth restriction
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
HNNE—Hammersmith Neonatal Neurologic Examination
NNNS—Neonatal Intensive Care Unit Network Neurobehavioral Scale
PNS—postnatal corticosteroids
BPD—bronchopulmonary dysplasia

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THE NEUROBEHAVIORAL PERFORMANCE of preterm infants has been reported to differ significantly from term-born infants by term equivalent age (37–42 weeks' postmenstrual age [PMA]), but most of these studies have contained few very immature infants,[1–6] been limited in exploring the perinatal correlates of abnormal behavior in the newborn period, and differed in the underlying variables reported to be important. Several studies have suggested that gestational age (GA) is an important factor,[1,7,8] whereas other studies have reported minimal effects of GA on neurobehavior at term.[4,6,9,10] In one study, race was important,[7] whereas cranial ultrasound abnormalities were the most important in another.[8] Growth-restricted preterm infants are reported to have poorer attention-interaction abilities[11] and poorer neurobehavioral scores,[10] although the latter study also included some term infants. Thus, the aims of this study were to describe the nature of alterations in very preterm infant neurobehavior at term compared with term-born controls and to examine the influence of perinatal variables on altered patterns of neurobehavior in an unselected group of very preterm infants, assessed using 2 standardized neonatal examinations at term-equivalent age.

PATIENTS AND METHODS

Study Sample

This was a prospective study of very preterm infants (GA <30 weeks or birth weight <1250 g) from the Royal Women's and Royal Children's Hospitals in Melbourne, Victoria, Australia, recruited between July 2001 and April 2004. Term control infants were recruited during the same period from births in the Royal Women's Hospital and from community antenatal classes. The study was approved by the research and ethics committees at the Royal Women's Hospital, and informed written consent was obtained from the infants' parents.

Perinatal Data Collection

Extensive perinatal data (Table 1) were collected by a research nurse. Weight *z* scores were computed relative to the British growth reference[12] with intrauterine growth restriction (IUGR) defined as a birth weight *z* score of less than −2 SD. Cranial ultrasounds were completed throughout the primary hospitalization, at a minimum of 1 to 3 days of age, at 1 week of age, and then monthly until discharge. Intraventricular hemorrhage (IVH) was graded according to the criteria of Papile et al.[13] Total assisted ventilation was defined as the total number of days that an infant received either positive pressure ventilation (either intermittent or high-frequency) via an endotracheal tube and/or nasal continuous positive airways pressure. Infants with either proven or suspected necrotizing enterocolitis (NEC) were coded as having NEC. An infant who was receiving any amount of breast milk at the time of discharge to home was coded as "breast milk at discharge." Data collected at the term neurobehavioral examination included the infant's PMA, current weight, and head circumference.

TABLE 1 **Infant Characteristics and Perinatal Exposures in 157 Preterm Infants**

Variable	*N* (%)	Range
Birth weight, g	965 (225)[a]	450 to 1500
Gestational age, wk	27.6 (2.0)[a]	22 to 32
Birth weight *z* score	−0.7 (1.0)[a]	−4.0 to 1.8
Days of assisted ventilation, *N*	27	17.8 (0 to 109.2)[b]
Days of parenteral nutrition, *N*	12.5	10 (0 to 176)[b]
Birth weight <1000 g	91 (58.0)	
Gestational age <27 wk	50 (31.8)	
IUGR, birth weight *z* score less than −2 SD	18 (11.5)	
Male	82 (52.2)	
Multiple birth	68 (43.3)	
Antenatal corticosteroids	139 (88.5)	
Postnatal corticosteroids	9 (5.7)	
Patent ductus arteriosus	78 (49.7)	
Oxygen dependency at 36 wk	49 (31.2)	
IVH grade 3 or 4	10 (6.4)	
Proven or suspected necrotizing enterocolitis	13 (8.3)	
Breast milk at discharge	71 (45.2)	

[a] Mean (SD).
[b] Median (range).

Term Neurobehavioral Evaluations

Neurobehavioral examinations of infants were completed at term equivalent age (37–42 weeks' PMA) at the Royal Children's Hospital. Occasionally preterm infants who were still inpatients at term equivalent age were assessed in their nurseries. Two standardized neurobehavioral evaluations were completed on each infant: (1) the Hammersmith Neonatal Neurologic Examination (HNNE)[14] and (2) the NICU Network Neurobehavioral Scale (NNNS).[15] Two different evaluations were used so that their practical applications and relationships to perinatal exposures could be compared.

These assessments were chosen because they can be administered at term equivalent age, and they were both designed to include the assessment of high-risk infants. Data have been published previously on the performance of preterm infants in the neonatal period, assessed using the HNNE[6] and the NNNS.[16] These neonatal assessments were also chosen because they differ from each other in several ways. The HNNE is neurologically based, and the NNNS is neurobehaviorally based. The HNNE is currently used more frequently in the clinical setting than the NNNS and may be attractive to clinicians in the neonatal unit, because it is relatively brief and can be self-taught from the manual. The NNNS is a longer examination that has a large behavioral component and a summary section that is particularly relevant to preterm infants. This summary section includes items designed to capture infants' states of arousal and their

motor activity during the examination, their ability to use self-calming behaviors, the amount of physiologic reactivity displayed (such as color changes), and how much consoling is required from the examiner. Although another assessment, the Assessment of Preterm Infant Behavior, also includes many similar items and is designed expressly for use with preterm infants, it is a longer examination to administer than the NNNS, and it also takes considerably longer to score. All of the assessments for this study were video recorded to enable the review of examinations when necessary to clarify assessment scores.

HNNE

The HNNE was developed in 1981 by Dubowitz and Dubowitz[14] to assess the neurologic state of term and preterm infants. This assessment was designed for use in both research and clinical settings. The HNNE has 34 individual scores that are grouped into 6 subtotals: tone, tone patterns, reflexes, spontaneous movements, abnormal signs, and behavior. The sum of these 6 subtotals produces a total HNNE score.

An optimality score for term infants assessed with the HNNE was published in 1998,[17] and a revised (2nd) edition of this examination was published in 1999,[18] both of which have been used for the current study. The term optimality score is based on the distribution of raw scores from a population of 224 low-risk term infants between 6 and 48 hours old, with GAs between 37 and 42 weeks.[17] The performance of these term infants was compared with the performance of low-risk preterm infants (with normal neurologic outcomes at 18 months) at term equivalent age by Mercuri et al.[6] Two of the individual HNNE preterm infant median scores from Mercuri et al's[6] study would not be recoded as "optimal" when using the "term optimality" scores. The term optimality score for these 2 items for the purposes of this study were, therefore, widened to include the preterm median score, so that at least all of the median scores from Mercuri et al's[6] low-risk preterm infant population were recoded as optimal for the preterm infants in this study. All of the other individual items were recoded according to the published term optimality scores.

NNNS

The NNNS was developed by Lester and Tronick[15] for the Maternal Lifestyles Study to examine the effects of prenatal drug exposure on early neurobehavioral development. This assessment was designed to evaluate the neurologic integrity, behavioral functioning, and responses to stress or abstinence in high-risk infants.[19] The behavioral components of the NNNS were based on the well known Neonatal Behavioral Assessment Scale.[20] The NNNS has norms based on 125 term healthy infants (38–41 weeks' GA at birth) who were assessed using the NNNS within the first 2 days of life.[21] In addition, the NNNS has "quasi-norms" for preterm infants assessed at 1 month corrected age; however, these preterm infants were from a sample of infants at varying degrees of biological and/or social risk (many of whom were exposed to drugs prenatally).[16] The NNNS has 45 individual neurologic and neurobehavioral items that are clustered into state-dependent "packages," which are intended to be administered in a relatively invariant order; additionally, there are 21 individual summary items.[19] The habituation items and the stress/abstinence scale were not administered for the current study. Individual scores were coded and computed into 11 subscales/summary scores, namely: attention, handling, quality of movement, regulation, nonoptimal reflexes, arousal, hypertonicity, hypotonicity, asymmetrical reflexes, excitability, and lethargy.

Statistical Analysis

We hypothesized a priori that given the differences reported between preterm infants and term infants at term, very preterm infants (<30 weeks' GA or <1250 g) would also demonstrate alterations in neurobehavior by term and that these alterations would be influenced by factors known to be associated with poor long-term neurodevelopmental outcomes. These included events determined before birth (GA, gender, birth weight *z* score, and antenatal corticosteroids) and events occurring after birth (duration of assisted ventilation, NEC, grade 3 or 4 IVH, and receiving any breast milk at discharge).

All of the data were analyzed with SPSS 12.0.2 (SPSS Inc, Chicago, IL). Continuous variables were contrasted by *t* test, with equal variances not assumed. Neurobehavioral scores that were significantly skewed were dichotomized at the 25th or 75th percentile, depending on the direction of the score relative to normality (to be able to compare the one fourth with abnormal scores with the remaining three fourths with normal scores). Multivariate linear and logistic regressions were used to assess the influence of perinatal variables on HNNE and NNNS neurobehavioral scores where there were clinically important differences between preterm and term infants. We did not include the NNNS subscale hypertonicity, because we found that its current form of coding was not clinically useful, and the difference between the preterm and term groups was borderline ($P = .047$). Because these were exploratory analyses *P* values were not reduced for multiple testing.

RESULTS

Neurobehavioral examinations and perinatal data collection were completed on 168 infants, of whom there were complete perinatal data on 157 preterm infants at term equivalent age: they were a high-risk group as seen by their perinatal characteristics (Table 1). In contrast,

the 39 term infants had a mean birth weight of 3283 g (SD: 488) and mean PMA of 39.1 (SD: 1.2) weeks; 21 (54%) were male. Both groups were examined at similar PMAs (preterm, mean: 40.2 [SD: 1.2] weeks; term, mean: 40.6 [SD: 1.0] weeks). One preterm infant was too unwell at term to attempt an assessment.

Preterm Versus Term Infant Neurobehavior

Preterm infants performed poorly across all areas of the HNNE scales (the total and all subscales) compared with the term infants (Table 2). Likewise, for the NNNS, preterm infants performed poorly on 8 (of 11) NNNS summary scores, whereas the difference for 1 summary score (hypertonicity) was borderline. The remaining 2 summary scores, arousal and lethargy, did not distinguish clearly between preterm and term infant performances at term. Only the 8 NNNS summary scores, on which the preterm infants demonstrated significantly different neurobehavior compared with term infants, were used in the subsequent analyses with perinatal variables.

Influence of Perinatal Factors Within Preterm Infant Cohort

On univariate analysis of the relationships between neurobehavioral summary scores and perinatal variables, there were many statistically significant associations. The following variables were associated with significant reductions in the HNNE total score: days of assisted ventilation, grade III/IV IVH, postnatal corticosteroids (PNSs), PDA, lower GA, NEC, and smaller head circumference at term. The perinatal variables associated with most of the 6 HNNE subtotals and the 8 NNNS subscales tested were: days of assisted ventilation, 4 of 6 HNNE and 4 of 8 NNNS; grade III/IV IVH, 3 of 6 HNNE and 3 of 8 NNNS; PDA, 3 of 6 HNNE and 4 of 8 NNNS; lower GA, 2 of 6 HNNE and 4 of 8 NNNS; and birth weight, 2 of 6 HNNE and 3 of 8 HNNE. The remaining perinatal variables had fewer significant relationships with term neurobehavior. PNSs were associated with poor reflexes and poor spontaneous movements on the HNNE and worse nonoptimal reflex scores on the NNNS. Infants with IUGR had poorer self-regulation and quality of movement on the NNNS. Maternal antenatal corticosteroid administration was associated with improved global performance on the HNNE (ie, higher total scores) and better nonoptimal reflex scores on the NNNS. Receiving any breast milk at discharge was related to improved quality of movement and excitability scores on the NNNS. Female gender was also associated with better quality of movement scores (on the NNNS), whereas gender did not have a significant impact on HNNE scores.

Based on the univariate analyses and clinical interpretation, 8 perinatal variables were subsequently included in the multivariate statistical model, including GA, gender, IUGR (birth weight *z* score entered as a continuous variable), antenatal corticosteroids, days of assisted ventilation out of 10, proven or suspected NEC, grade III/IV IVH, and breast milk on discharge. The perinatal exposures associated with neurobehavior on multivariate regression are displayed in Fig 1 A and B, and significant findings ($P < .05$) are summarized in Table 3.

TABLE 2 Differences Between Preterm and Term Infant Neurobehavior at Term Equivalent Age

Total Scores	Preterm Infants	Term Infants	Mean Difference	95% Confidence Interval	P[a]
HNNE	*N* = 168	*N* = 39			
Tone	7.4	9.4	−1.9	−2.3 to −1.6	<.0001
Tone patterns	4.1	4.7	−0.6	−0.8 to −0.4	<.0001
Reflexes	5.4	5.8	−0.4	−0.6 to −0.3	<.0001
Spontaneous movements	2.0	2.8	−0.8	−1.0 to −0.7	<.0001
Abnormal signs	2.4	2.9	−0.5	−0.7 to −0.4	<.0001
Behavior	5.3	6.6	−1.2	−1.6 to −0.9	<.0001
HNNE to tal	26.6	32.3	−5.6	−6.5 to −4.8	<.0001
NNNS	*N* = 164	*N* = 39			
Attention[b]	5.6 (*n* = 150)	7.2 (*n* = 34)	−1.6	−2.0 to −1.2	<.0001
Handling[b]	0.4 (*n* = 152)	0.3 (*n* = 32)	0.1	0.0 to 0.2	.005
Quality of movement[b]	4.5 (*n* = 163)	5.7	−1.2	−1.4 to −1.0	<.0001
Regulation[b]	5.4 (*n* = 163)	6.9	−1.5	−1.8 to −1.2	<.0001
Nonoptimal reflexes	4.0	1.8	2.1	1.6 to 2.7	<.0001
Arousal[b]	3.9 (*n* = 163)	3.8	0.1	−0.1 to 0.4	.196
Hypertonicity	0.4	0.6	−0.3	−0.5 to 0.0	.047
Hypotonicity	0.2	0.0	0.2	0.1 to 0.3	<.0001
Asymmetrical reflexes	0.4	0.1	0.4	0.2 to 0.5	<.0001
Excitability	3.3	1.8	1.5	0.8 to 2.2	<.0001
Lethargy	3.9	3.3	0.6	−0.4 to 1.5	.225

[a] *P* value from independent samples *t* test with equal variances not assumed.
[b] Scales that require a minimum number of items and, hence, not all infants could be scored.

TABLE 3 **Summary of Significant ($P < .05$ or $P < .01$) Perinatal Variables in Multivariate Analyses Influencing Preterm Infant Neurobehavior at Term Equivalent Age**

Perinatal Variable	HNNE Subtotals/Total	NNNS Summary Scores
GA	+ve abnormal signs	NS
Gender (Female)	NS	+ve quality of movement
Birth weight *z* score	NS	NS
Antenatal Corticosteroids	+ve tone	+ve nonoptimal reflexes
	+ve spontaneous movement	
	+ve total score	
Per 10 d of assisted ventilation	−ve reflexes	−ve nonoptimal reflexes[a]
	−ve spontaneous movements	−ve hypotonicity[a]
	−ve total score	
NEC	−ve tone[a]	NS
	−ve tone patterns	
	−ve total score[a]	
Grade 3 or 4 IVH	−ve tone	−ve attention
	−ve behavior	−ve nonoptimal reflexes
	−ve total score[a]	
Any breast milk at discharge		+ve regulation

+ve indicates positive influence on neurobehavioral score (ie, "better" neurobehavior); −ve, negative influence on neurobehavioral score (ie, "worse" neurobehavior); NS, not statistically significant ($P > .05$).
[a] $P < .01$.

HNNE

Multivariate regression analyses revealed that the perinatal variables most significantly associated with a reduced HNNE total score were: grade III/IV IVH ($P = .005$), proven or suspected NEC ($P = .006$), and duration of assisted ventilation ($P = .021$). Maternal antenatal corticosteroid administration, on the contrary, had a beneficial influence on the total HNNE score ($P = .010$). Within the HNNE subscales, grade III/IV IVH had the most significant influence on altered tone ($P = .011$) and behavior ($P = .045$). Proven or suspected NEC was also associated with altered tone ($P = .008$) and tone patterns ($P = .020$). The duration of assisted ventilation was most significantly related to poor spontaneous movements ($P = .013$), whereas antenatal corticosteroids had a positive influence on spontaneous movements ($P = .032$) and tone ($P = .037$). Altered reflexes were also related to the duration of assisted ventilation ($P = .034$). In this multivariate model, higher GAs remained significantly associated only with better scores for abnormal signs ($P = .040$), whereas the effect of IUGR (birth weight *z* score) on HNNE scores became nonsignificant. Gender continued to have no statistically significant impact on any HNNE scores.

NNNS

The total number of days of assisted ventilation had the greatest impact on preterm infant neurobehavioral performance on the NNNS at term. A longer duration of assisted ventilation was associated with increased nonoptimal reflexes ($P < .001$) and hypotonicity ($P = .012$). Grade III/IV IVH was also associated with worse attention scores ($P = .024$) and more nonoptimal reflexes ($P = .039$). Maternal antenatal steroid administration continued to have a beneficial influence on neurobehavior, relating to better scores on nonoptimal reflexes ($P = .024$). Receiving any amount of breast milk on discharge to home also had a beneficial influence on neurobehavior at term, specifically on self-regulation capacities (regulation, $P = .036$). Gender continued to have a significant effect on quality of movement only, with girls performing better than boys ($P = .023$).

Although GA had significant effects on NNNS neurobehavior on univariate analysis (nonoptimal reflexes, $P = .001$; hypotonicity, $P = .003$; and lethargy, $P = .025$), all of these relationships became nonsignificant on multivariate analysis. Similarly, birth weight *z* scores, which related to poor regulation and poor quality of movement on univariate analysis, no longer had a significant influence on NNNS neurobehavior. The NNNS subscales of asymmetrical reflexes, excitability, and handling were not significantly affected by perinatal factors included in this multivariate regression model.

DISCUSSION

This study has demonstrated that very preterm infants differ significantly across many functional neurobehavioral domains at term-corrected age compared with their term-born peers using 2 standardized neonatal assessments, the HNNE (more neurologically based) and the NNNS (more neurobehaviorally based). On both the NNNS and the HNNE, preterm infants had significantly greater suboptimal reflexes, abnormal muscle tone (particularly hypotonicity, with extensor patterns frequently observed), poor quality of movement and poor spontaneous movement, and abnormal signs (such as startles and tremors), as well as a decreased capacity to attend to visual and auditory stimuli. Furthermore, our study revealed significant associations between many perinatal variables and preterm infant neurobehavior at term that

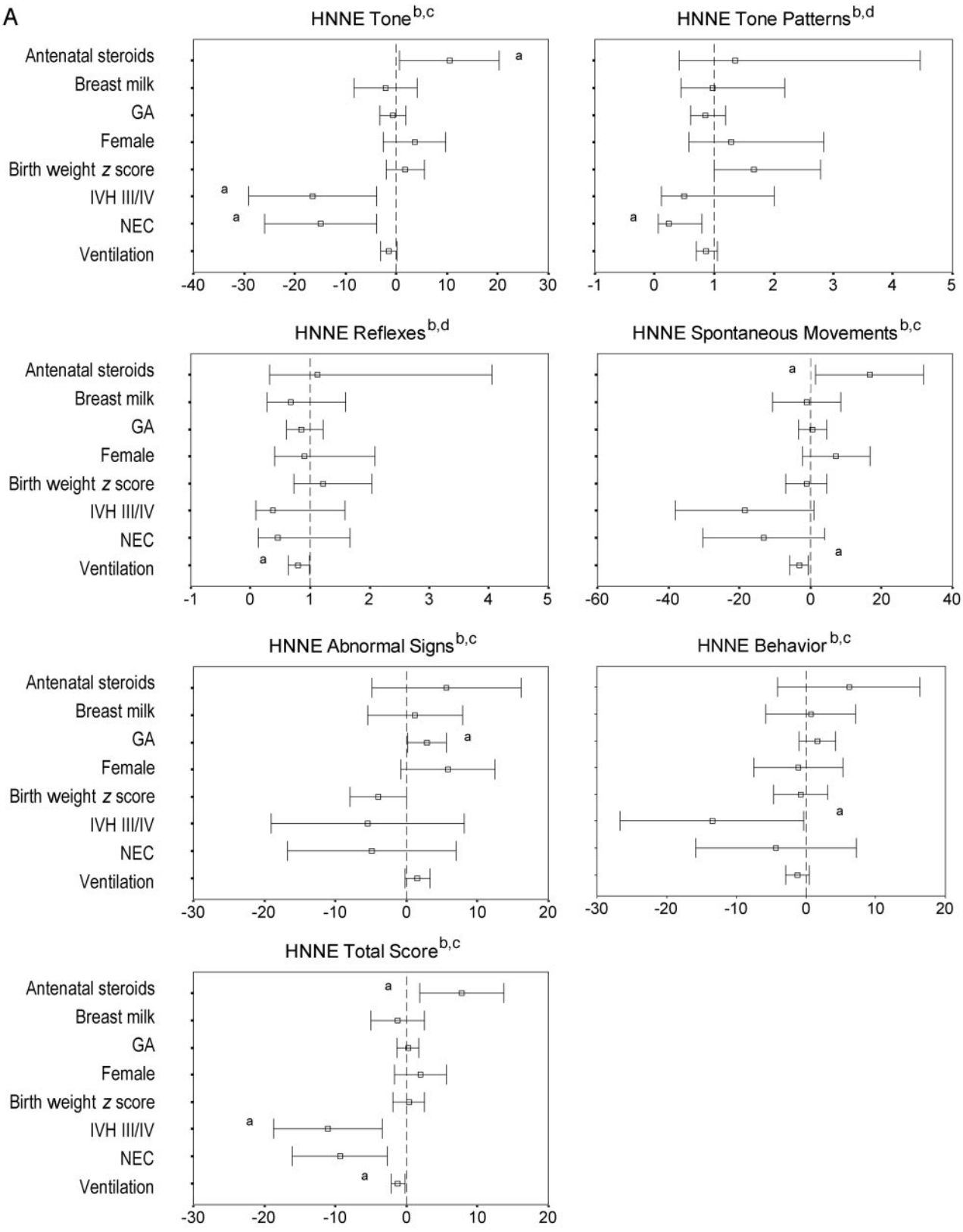

FIGURE 1

A, graphs indicating the influence of perinatal variables in multivariate analyses on preterm infants' neurobehavioral scores on the HNNE at term. B, Graphs indicating the influence of perinatal variables in multivariate analyses on preterm infants' neurobehavioral scores on the NNNS at term. Ventilation indicates the total number per 10 days of assisted ventilation. [a] Confidence intervals for statistically significant variables do not cross the vertical dotted line. [b] Relative neurobehavioral scores. [c] Mean difference and 95% confidence intervals. [d] Odds ratios and 95% confidence intervals.

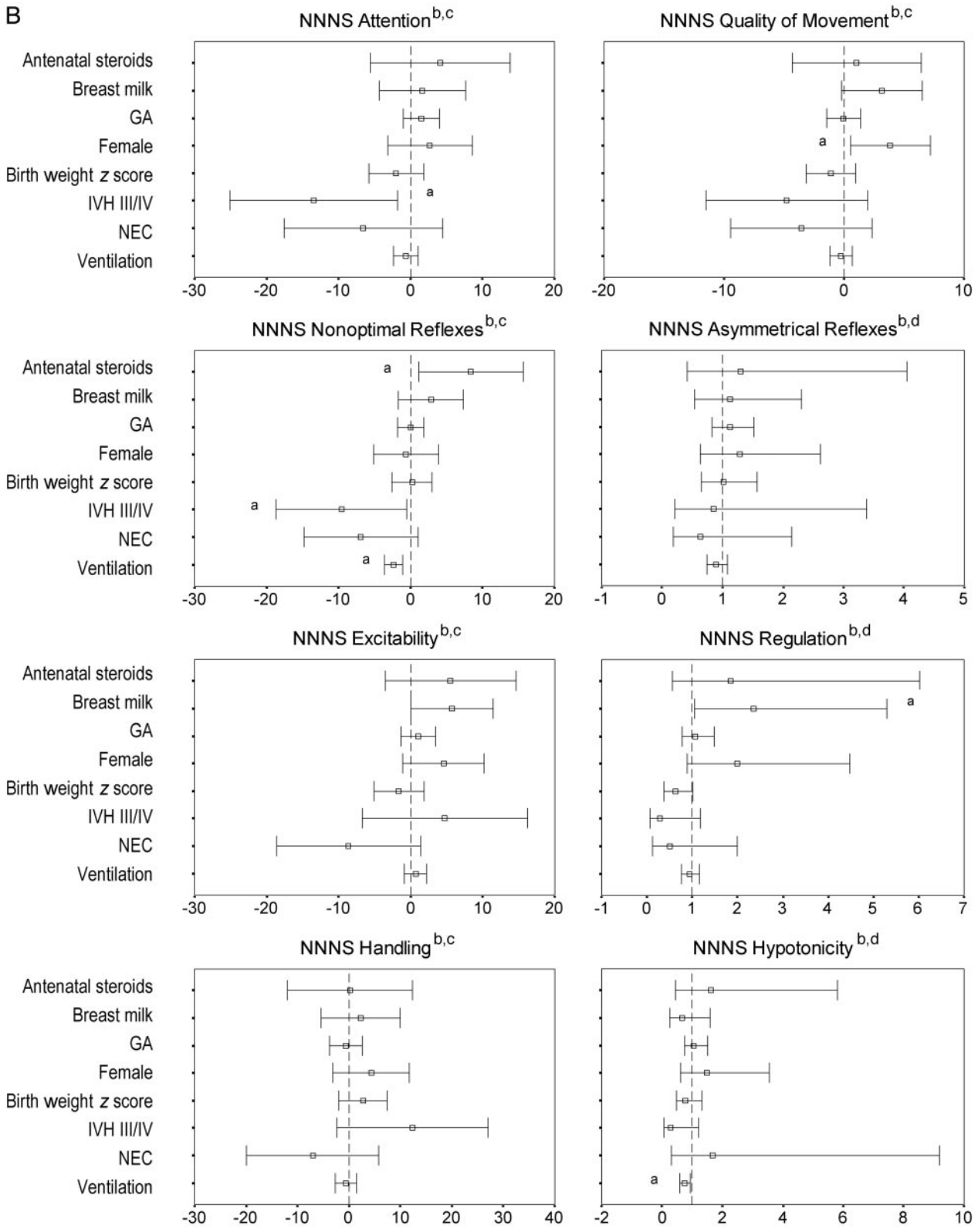

FIGURE 1
Continued

persisted after adjustment for confounding variables. In particular, the duration of assisted ventilation, grade III/IV IVH, and proven or suspected NEC were significantly associated with poorer neurobehavioral performances at term. Receiving breast milk at discharge and administration of antenatal corticosteroids had positive

influences on neurobehavior at term. We did not find a significant impact of immaturity independent of the severity of medical exposures.

There are several limitations to this study that are important to note. The term optimality score was used to recode the raw HNNE scores in this study. We acknowledge that a preterm optimality score may have been more appropriate, because preterm infants seem to have a wider range of scores on the HNNE at term equivalent age than their term peers, particularly for items pertaining to muscle tone and behavior. Thus, because there are currently no preterm infant norms per se, we took into account the term medians published by Mercuri et al[6] (based on 157 preterm infants with normal neurodevelopmental outcomes at 18 months' corrected age) in an attempt to make the recoding of our raw scores more relevant to the infants in our study. Similarly, the NNNS does not have normative data for preterm infants at 40 weeks' corrected age. Although this assessment, in line with other standardized neonatal assessments, distinguishes clearly between preterm and term infant neurobehavior at term, the current recoding may not do justice to the summary scores of lethargy, arousal, and hypertonicity for preterm infants.

A further limitation occurs with the issue of examiners remaining blind to the status (term versus preterm) of infants whom they are examining. It has been noted previously that it is difficult for examiners (particularly experienced examiners) to remain blind to an infant's status in such studies.[4,22] Although the examiner in our study (N.B.) was blind to infants' neonatal histories, it is possible that examiner bias, in either direction, may have contributed to some of the findings when comparing preterm and term infant neurobehavior. Such a bias would not have occurred, however, when exploring the relationships of various perinatal variables on neurobehavior within the preterm cohort alone.

Finally, we are aware that the results of our analyses are conditional on the completeness of the statistical model that we have used. In conjunction with univariate analyses, we have selected variables that were felt to be clinically important to the early development of very preterm infants. However, this model does not explain all of the variation that we have observed between the perinatal variables and preterm infant neurobehavior at term. We speculate that there are influences outside of this model, such as alterations in brain structure[23] and noncystic white matter injury (that can be more accurately detected by MRI than cranial ultrasound),[24] that may further explain poor neurobehavior in the very preterm infant at term. Social factors, such as parental education and socioeconomic status, may be influential, and the extrauterine environment, beyond medical exposures, may also play a role.

Defining Differences in Neurobehavior in Preterm Infants

Despite these limitations, our findings in preterm infants of poorer neurobehavioral performances compared with term infants are consistent with recently published studies using standardized neonatal examinations at term.[2–6] The major difference between our study and others is that the mean GA of our preterm infant cohort was generally much lower than these previously published studies.

The 2 neurobehavioral tools that we used both documented significant disturbances in motor behavior and alterations in tone. The NNNS subscales distinguish low tone from increased tone, but the HNNE scales do not. The NNNS has additional behavioral summary scores versus the HNNE, such as regulation, excitability, arousal, and lethargy. We found that preterm infants had significantly poorer self-regulation capacities and significantly higher excitability scores. The NNNS excitability summary score reflects an infant's state, motor and physiologic responses to handling, irritability, and consolability. We observed preterm infants to have greater motor disorganization, irritability, and physiologic compromise than term infants. Preterm infants were also more difficult to console. Although the NNNS scores for lethargy and arousal did not reflect significant differences between preterm and term infants, we found that there was a trend for preterm infants to have more extreme arousal responses compared with term infants. There was also a trend for preterm infants to have higher lethargy scores, which included low responses to visual and auditory stimuli. The NNNS was originally developed for the evaluation of the drug-dependent infant; with modification to the current syntax (which calculates the NNNS summary scores), these items could become more sensitive for evaluating preterm infants.

Perinatal Influences on Altered Preterm Neurobehavior Within Preterm Infants

Our study adds further information to the attempt to unravel the pathway to alterations in infant neurobehavior in the preterm infant by analyzing the perinatal exposures that were most strongly associated with performance. Previous studies that have addressed this issue have not always found evidence of any clear relationships between perinatal factors and neurobehavior, but differences in study design may account for these discrepancies. Jeng et al[4] studied a smaller sample using the Neonatal Neurobehavioral Examination-Chinese version, which has a simplified scoring system with only 3 options: responses expected at term, responses expected at 32 to 36 weeks, and responses expected at <32 weeks. Our univariate findings are more similar to a recent study by Martens et al,[25] where smaller birth weights, IUGR, and administration of PNS were significantly associated with poor neurobehavioral performances at term on univariate analysis using Prechtl's neurologic

examination. Our study confirmed these relationships on univariate analysis but, in addition, also found significant associations between poor neurobehavior and prolonged ventilation, PDA, NEC, and IVH. Likewise, Korner et al[26] have also reported significant associations between preterm infant medical complications and neonatal neurobehavioral performance (while adjusting for PMA).

The relationship between perinatal variables and preterm infant neurobehavior at term is complex, with multiple confounding elements, and, thus, in an attempt to control for competing influences, we chose to examine the data using a multivariate regression model. On entering 8 perinatal variables into this model, we continued to demonstrate that perinatal exposures were related significantly to altered patterns of neurobehavior. Medical therapies and severity of illness had a more significant effect on neurobehavioral performance than demographics such as gender, GA, and birth weight *z* score. Grade III/IV IVH and the total number of days of assisted ventilation (intermittent positive pressure ventilation plus continuous positive airways pressure) seemed to have the most significant negative impact on neurobehavior, followed by proven or suspected NEC.

Comparisons with similar studies are limited by numerous factors, the greatest being inconsistencies in the selection of perinatal variables included in statistical models. Perhaps the most recent comprehensive studies to have also examined the influence of multiple perinatal variables on preterm infant neurobehavior at term are those by Jeng et al,[4] Martens et al,[25] and Sanchez-Stopiglia et al.[8] Sanchez-Stopiglia et al[8] reported univariate correlations between the degree of intracranial hemorrhage (intraventricular and periventricular) and neurobehavior using the HNNE at term, which did not persist on multivariate analysis for the presence of any other brain abnormality. In contrast, we found that IVH in the neonatal period continued to have the most global negative effect across many neurobehavioral domains on both the HNNE and NNNS on multivariate analysis.

Assisted ventilation and proven or suspected NEC, in general, affected neuromotor responses rather than behavioral responses. The total number of days of assisted ventilation additionally affected spontaneous movements. It is interesting to note that Perlman and Volpe[27] have previously described altered movement patterns in preterm infants with severe bronchopulmonary dysplasia ([BPD] emerging around 2–3 months' corrected age) who had an extrapyramidal movement disorder consisting of rapid, random, jerky movements. Martens et al[25] also found, on multivariate analysis, that respiratory illness (BPD) had a significant influence on neurobehavior, and Jeng et al[4] reported that prolonged ventilation and oxygen therapy had borderline effects (neither studies included NEC in their multivariate analysis). Although PNSs were significantly associated with poor neurobehavior on univariate analysis, they were not included in our multivariate regression model, because they were only received by 6% of preterm infants in this study.

Infants with these perinatal risk factors (BPD, IVH, and NEC) are also more likely to have a longer hospitalization, again possibly contributing to their increased risk of altered neurobehavior. The contribution of these risk factors to altered neurobehavioral performance at term is not unexpected, but our data are unique in confirming this risk using 2 different neonatal assessments in a very preterm infant cohort; both assessments demonstrated significant relationships, with each perinatal exposure producing a slightly different pattern of altered neurobehavior.

Outcome studies of preterm infants have reported similar perinatal risk factors for neurodevelopmental morbidity in later childhood, including cranial ultrasound abnormalities (notably, IVH grades III and IV),[28–34] prolonged assisted ventilation (or BPD or chronic lung disease),[30,31,34–41] and NEC (particularly NEC requiring surgery).[31,39,42,43] Our findings, however, suggest that alterations in very preterm infant neurobehavior, associated with these risk factors, are more immediate and are detectable as early as term equivalent age. Preterm infants with poor neurobehavior at term were often more difficult to handle, harder to socially engage without causing state and motor disorganization and/or physiologic compromise, and frequently had limited capacity for self-regulation and were more difficult to console. The additional behavioral items on the NNNS were particularly useful for recording these neurobehavioral characteristics and may provide helpful information when planning developmentally supportive care. As has been suggested recently, parents of infants with such disturbances in neurobehavior may need support and guidance in the modification of their caregiving practices to adapt to their infant's neurobehavioral characteristics.[44] In addition, the HNNE and the NNNS may provide helpful information for referrals to early intervention and/or preterm infant follow-up programs.

Not all of the perinatal variables explored had a negative affect on the early neurobehavior of very preterm infants. We found that antenatal corticosteroids had a positive influence on neuromotor responses (spontaneous movements and nonoptimal reflexes), as well as the total HNNE score. Receiving any breast milk either orally (breastfeeding or bottle) or via a nasogastric or gastrointestinal tube at the time of discharge to home had a positive influence on levels of excitability and self-regulation capability. It may not be breast milk per se that is important; for example, the amount of time and handling infants received from their mother may be the mechanism for improving neurobehavior. Gender and GA had less influence on neurobehavior at term than perinatal exposures and neonatal illness. There were no

statistically significant associations with birth weight *z* score when controlling for other influences using multivariate analysis.

CONCLUSIONS

Very preterm infants at term equivalent age show abnormalities in motor behavior and higher cortically integrated functions, such as orientation and attentional abilities. We found that many medical therapies or variables reflecting severity of illness were associated with abnormal neurobehavior after adjusting for multiple perinatal factors; we are, therefore, currently assessing neurodevelopmental outcome at 2 years of age in this cohort to study the longitudinal outcomes. Our study suggests that neurobehavioral examination at term equivalent age is a useful tool for evaluating the impact of neonatal intensive care.

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