PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Sleep-Wake Transitions in Premature Neonates Predict Early Development

Omri Weisman, Reuma Magori-Cohen, Yoram Louzoun, Arthur I. Eidelman and Ruth Feldman

Pediatrics 2011;128;706; originally published online September 12, 2011;
DOI: 10.1542/peds.2011-0047

Sleep-Wake Transitions in Premature Neonates Predict Early Development

WHAT'S KNOWN ON THIS SUBJECT: Sleep organization is a central index of neuromaturation in premature neonates and has been shown to predict short-term outcomes, particularly cognitive development. However, little is known about the relationships between sleep organization in neonates and long-term outcomes across multiple developmental domains.

WHAT THIS STUDY ADDS: A new approach used mathematical clustering of sleep-state transitions. Infants who cycled mainly between quiet sleep and wakefulness showed greater neuromaturation, lower negative emotionality levels, better cognitive development, and better symbolic, verbal, and executive capacities at 5 years.

abstract

OBJECTIVE: To identify patterns of sleep-wake transitions in the neonatal period that might differentiate premature infants who would show better or worse outcomes in multiple developmental domains across the first 5 years of life.

METHODS: Participants were 143 low birth weight premature infants (mean birth weight: 1482 g; mean gestational age [GA]: 31.82 weeks). Sleep states were observed at a GA of 37 weeks in 10-second epochs over 4 consecutive evening hours and were analyzed through mathematical clustering. Neurobehavioral maturation was evaluated with the Neonatal Behavior Assessment Scale at discharge, emotional regulation was assessed during infant-mother and infant-father interactions at 3 and 6 months, cognitive development was measured at 6, 12, and 24 months, and verbal IQ, executive functions, and symbolic competence were tested at 5 years.

RESULTS: Three types of state-transition patterns were identified, and no differences in birth weight, GA, or medical risk between the 3 groups were found. Infants whose sleep-state transitions were mainly characterized by shifts between quiet sleep and wakefulness exhibited the best development, including greater neonatal neuromaturation, less negative emotionality, better cognitive development, and better verbal, symbolic, and executive competences at 5 years. In comparison, infants who cycled mainly between states of high arousal, such as active sleep and cry, or between short episodes of active and quiet sleep showed poorer outcomes.

CONCLUSIONS: Defining sleep organization on the basis of transitions between states proved useful for identifying risk and resilience indicators in neonatal behavior to predict trajectories of neurobehavioral, emotional, and cognitive growth. *Pediatrics* 2011;128:706–714

AUTHORS: Omri Weisman,[a] Reuma Magori-Cohen, MA,[b] Yoram Louzoun, PhD,[b,c] Arthur I. Eidelman, MD,[d] and Ruth Feldman, PhD[a,c]

Departments of [a]Psychology and [b]Mathematics and [c]Gonda Brain Sciences Center, Bar-Ilan University, Ramat-Gan, Israel; and [d]Department of Pediatrics, Shaare Zedek Medical Center and School of Medicine, Hebrew University, Jerusalem, Israel

KEY WORDS

sleep-wake patterns, prematurity, longitudinal studies, cognitive development, executive functions

ABBREVIATIONS

MDI—Mental Developmental Index
PDI—Psychomotor Developmental Index
GA—gestational age
AUC—area under the curve

Mr Weisman and Ms Magori-Cohen contributed equally to this work.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0047

doi:10.1542/peds.2011-0047

Accepted for publication Jun 8, 2011

Address correspondence to Ruth Feldman, PhD, Department of Psychology and the Gonda Brain Sciences Center, Bar-Ilan University, Ramat-Gan 52900, Israel. E-mail: feldman@mail.biu.ac.il

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Premature birth places infants at greater risk for neurobehavioral, cognitive, and social-emotional difficulties, and infants born preterm often exhibit more attention and learning disorders, conduct problems, emotional dysregulation, and poor cognitive functioning across childhood and adolescence.[1–7] However, the population of low birth weight, premature infants is highly heterogeneous; whereas some children may show major developmental delays, others may follow a more-typical developmental course.[2,8,9] Because early detection and intervention for those at greatest risk are of prime clinical importance, the ability to identify risk and resilience indicators that could be detected in the neonatal period and could predict developmental outcomes for premature infants would be of much clinical relevance.

Among the central markers of neurodevelopmental maturation in premature infants is the organization of sleep.[10,11] Premature birth disrupts the consolidation of the biological clock,[12] and preterm infants often show disorganized sleep, expressed in greater proportions of indeterminate states,[13] poor sleep-wake cyclicity,[14] and short sleep bouts.[13–15] Intervention programs such as skin-to-skin contact and the "breathing bear," which provide external thermal or rhythmic organization to the infant's immature state control, were found to increase both neurologic maturation and sleep organization.[16–18] In turn, sleep organization is thought to provide the foundation for the development of physiologic maturation, arousal regulation, and cognitive growth.[13,19–23]

Sleep organization among premature neonates has been associated with short-term developmental outcomes. Higher Mental Developmental Index (MDI) scores at 6 months were related to decreases in nighttime sleep proportions at gestational ages (GAs) of 32 to 36 weeks.[24] MDI scores for high-risk premature infants at corrected age of 24 weeks were associated with the development of quiet sleep in the early night and those at 52 weeks with greater stability of the longest episode of sustained sleep.[20] Similarly, associations were found between the amount of rapid eye movement sleep at a GA of 37 weeks and MDI scores at 6 months.[25]

Despite research pointing to the centrality of sleep organization, the effects of neonatal sleep patterns on long-term outcomes have received little research, and most studies did not measure developmental outcomes beyond infancy.[20,22,23,26–28] Furthermore, although sleep is thought to provide the basis for regulation of arousal and emotion,[29] little is known about the possible links between neonatal sleep patterns and the development of emotional, social, and regulatory competences.[16,30,31] Finally, most studies examined the proportions or durations of sleep states,[32] and the temporal organization of sleep has received significantly less empirical attention.

Therefore, the present study focused on the organization of sleep states, in particular the pattern of transitions between sleep and wake states, as a potential marker of optimal versus high-risk development. The transition between sleep and wakefulness is a central feature of the biological clock in humans and mammals and serves as an index of central nervous system maturity.[12] We examined 3 patterns of state transitions in relation to infants' neurobehavioral profiles at term age. We hypothesized that premature neonates whose sleep was characterized by more-organized transitions between quiet sleep and wake states, denoting greater consolidation of the biological clock, would show better development across functional domains. In contrast, sleep organization that was characterized predominately by transitions between highly aroused states, such as active sleep and cry, would mark more-dysregulated neurobehavioral development and would predict a poorer developmental course in early childhood.

METHODS

Participants

Participants included 143 low birth weight, premature infants (mean GA: 31.82 weeks [range: 25–34 weeks]) drawn from a consecutive birth sample of infants born at a tertiary care medical center in Jerusalem, Israel. To eliminate potential confounders, only mothers who were $>$20 years of age, were married to the infant's father, and had completed $\geq$12 years of schooling were included. Mothers were between 21 and 42 years of age (mean: 28.96 years [SD: 5.40 years]) and had completed between 12 and 20 years of education (mean: 14.11 years [SD: 2.18 years]). Fathers were between 24 and 45 years of age (mean: 32.12 years [SD: 6.23 years]) and had completed between 12 and 25 years of education (mean: 14.05 years [SD: 2.79 years]). The sample included 138 Israeli-Jewish families and 5 Israeli-Arab families; all were considered middle class by Israeli standards.[33] The study was approved by the Shaare Zedek Medical Center institutional review board, and all parents provided informed consent.

Infants were excluded if they had grade III or IV intraventricular hemorrhage, perinatal asphyxia, or a metabolic or genetic disease or were still undergoing ventilation at a GA of 37 weeks. Infants' medical risk was quantified on the basis of Clinical Risk Index for Babies scores.[34] According to departmental policy, infants were not discharged while receiving theophylline or caffeine medications; therefore, sleep patterns were evaluated when infants were not under the influence of such medications. At 2 years, children underwent thorough neurologic examinations, no sleep-disordered breathing symptoms were reported by the parents, and medical examinations did not detect any respiratory abnormalities. It is important to note that our exclusion criteria, which eliminated infants with maternal/social factors or medical conditions known to correlate with poor outcomes, enhance the clinical importance of the study by attempting to distinguish infants at risk for developmental difficulties among preterm infants born at relatively low risk. Infants were tested at a GA of 37 weeks in the hospital, at 3 months in their homes, and at 6, 12, and 24 months and 5 years in the laboratory.

Sleep-State Transitions and Neurobehavioral Maturation in Neonatal Period

State Observation

Before discharge (GA of 37 weeks), infant sleep states were observed in 10-second epochs for 4 consecutive evening hours (7 PM to 11 PM) by trained observers, who entered the data into a computerized program. Consistent with previous research,[35,36] states included quiet sleep, active sleep, sleep-wake transition, unfocused alertness, alert wakefulness, and cry.

Typologic Features of Sleep-State Transitions

Mathematical clustering of sleep transition patterns was computed on the basis of the fraction of transitions between states and not on the basis of the proportion of time spent in each state. For each pair of states, we measured P_{ij}, the probability of transition from state *i* to state *j*. To estimate the transition probability, we first assessed the probability of state *i* being followed by state *j*. This transition probability can be defined as an absolute probability, that is, the probability of state *i* at time *t* and state *j* at time $t + 1$. In such a case, the probability is defined simply as the fraction of following observation pairs with states *i* and *j*, $K_{i,j}$, divided by the total number of state pairs, that is, $P_{ij} = K_{i,j}/\Sigma K_{i',j'}$. Thirty-six transition probabilities were calculated for the 4-hour observation for each of the 143 infants. The resulting matrix was then treated as a 36-dimension vector, and a *k*-means clustering algorithm was applied to the vectors with $k = 3$ and a correlation distance defined as the correlation between the 36 values in the matrix (ie, the probability matrix for each infant was treated as a 36-dimension vector, and 1 − correlation between the vectors for different infants was defined as the distance between them). Because of their low frequencies, the 3 wake states, that is, sleep-wake transition, unfocused alertness, and alert wakefulness, were combined into a single wake state. Therefore, the final clusters were computed on the basis of a 4-state matrix including quiet sleep, active sleep, wake, and cry, and all subsequent analyses were based on this 4-state matrix.

Three clusters of sleep-wake transitions emerged from analysis of the 4-state matrix (Fig 1), and infants were divided into 3 groups according to the nature of their sleep-wake transitions. The distributions of all transitions related to these 4 states are presented below for each group.

Cluster 1 included high-arousal transitions ($N = 47$). In this group, most of the transitions involved states of high arousal (active sleep or cry), with 83% of the transitions being within or between active sleep and cry. Distributions of such transitions were as follows: 23% between active sleep and cry, 24% within active sleep, 18% between active sleep and quiet sleep, 13% between cry and wake, and 5% within cry. The remaining 17% of transitions were as follows: 5% between active sleep and wake, 0.5% between quiet sleep and wake, 0.5% between quiet sleep and cry, 9% within wake, and 2% within quiet sleep.

Cluster 2 included organized sleep-wake transitions ($N = 38$). In this group, 66% of transitions were between or within low-arousal sleep and wake states (quiet sleep or wake). The distribution of such transitions was as follows: 25% between quiet sleep and wake, 25% within quiet sleep, and 16% within wake. The remaining 34% of transitions were as follows: 10% between active sleep and quiet sleep, 6% between wake and cry, 6% between

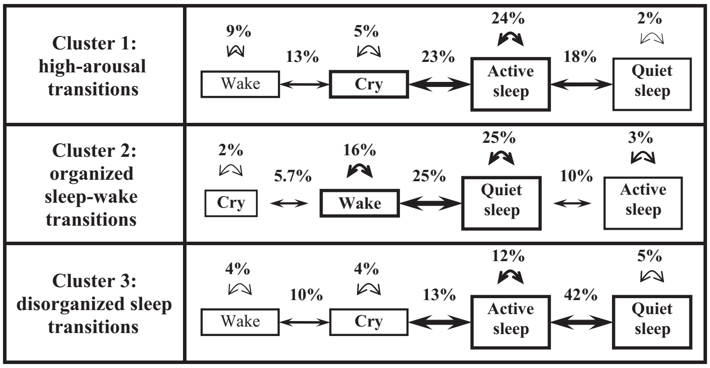

FIGURE 1

Three clusters depicting patterns of transitions between the 4 neonatal states among low birth weight premature infants in the neonatal period. Clusters are based on probabilities of transitions between states.

wake and active sleep, 3% between active sleep and cry, 4% between cry and quiet sleep, 3% within active sleep, and 2% within cry.

Cluster 3 included disorganized sleep transitions ($N = 58$). In this group, 59% of transitions were between or within sleep states (active sleep or quiet sleep), with 42% being between active sleep and quiet sleep, 12% within active sleep, and 5% within quiet sleep. The remaining 41% of transitions were as follows: 13% between active sleep and cry, 10% between wake and cry, 6% between active sleep and wake, 3% between quiet sleep and cry, 1% between quiet sleep and wake, 4% within wake, and 4% within cry.

Clusters were formed without information about the infant's subsequent development, and follow-up assessments were conducted by people who were blinded to the infants' cluster membership. The overall proportions of time infants in each group spent in the 4 states (quiet sleep, active sleep, wake, and cry) are presented in Table 1, and group differences are reported.

Neurodevelopmental Status

Infants were examined with the Neonatal Behavior Assessment Scale, by a trained neonatologist. Items were grouped into 6 clusters,[37] and the orientation, range of state, and regulation of state clusters were used.

Infant Negative Emotionality at 3 and 6 Months

Infants were visited at home at corrected age of 3 months and were videotaped interacting with their mothers and fathers for 5 minutes each. At 6 months, infants were videotaped interacting with their mothers in the laboratory. Interactions were coded with the Coding Interactive Behavior scale,[38] a rating system for adult-child interactions that includes multiple codes that are rated from 1 to 5 and are aggregated into several composites. The Coding Interactive Behavior scale was well validated in multiple studies of healthy and high-risk infants and showed good psychometric properties.[30,39–42] Consistent with previous work,[43] infant negative emotionality was considered the average of infant fussiness, infant fatigue, infant withdrawal, and gaze aversion scores. Two coders, who were blinded to other information, were trained to 90% agreement. Reliability, which was measured with 15 infants at each stage, averaged 96% ($k = 0.86$). Negative emotionality scores with the mother and father ($r = 0.53$; $P < .001$) and those at 3 and 6 months ($r = 0.39$; $P < .001$) were correlated, and the 3 scores were averaged into a negative emotionality score.

Cognitive Development Across Early Childhood

Trained psychologists assessed the infants' development with the Bayley Scales of Infant Development II,[44] at corrected ages of 6, 12, and 24 months. The Bayley Scales of Infant Development II yields 2 scores, the MDI and the Psychomotor Developmental Index (PDI). Children were tested with the Wechsler Preschool and Primary Scale of Intelligence[45] at 5 years of age, and verbal IQ scores were used. Different psychologists tested the children at each age, to ensure unbiased evaluations. Testers at each age were blinded to the results of previous evaluations.

Executive Functions and Symbolic Competence at 5 Years

Executive Functions

The executive function domain of the Developmental Neuropsychological Assessment test[46] was administered.

Symbolic Competence

Children's symbolic competence was coded on the basis of 10 minutes of mother-child play with predetermined toys. Sessions were coded in 10-

TABLE 1 Neonatal Information According to Sleep-State Cluster Group

	High Arousal (Cluster 1) ($N = 47$)	Organized Sleep-Wake (Cluster 2) ($N = 38$)	Disorganized Sleep (Cluster 3) ($N = 58$)	χ^2/U
Weight, mean ± SD, g	1432 ± 356	1496 ± 599	1511 ± 448	NS
GA, mean ± SD, wk	31.78 ± 3.04	31.65 ± 2.94	31.97 ± 3.20	NS
Clinical Risk Index for Babies score, mean ± SD	2.23 ± 2.82	1.79 ± 1.35	1.81 ± 2.86	NS
Male/female ratio	52/48	45/55	55/45	NS
Distribution of states, mean ± SD, %				
Quiet sleep	35.8 ± 20.9	32.8 ± 17.8	44.3 ± 19.1	6.08, cluster 2 < cluster 3[a]
Active sleep	39.8 ± 18.9	40.2 ± 19.2	29.5 ± 15.3	7.19, clusters 1 and 2 > cluster 3[a]
Cry	4.8 ± 8.7	5.1 ± 6.2	3.1 ± 2.7	NS
Wake	19.6 ± 19.2	21.9 ± 18.2	23.1 ± 16.6	NS
Neonatal Behavior Assessment Scale score, mean ± SD				
Orientation	5.19 ± 0.85	5.95 ± 0.98	4.96 ± 0.86	5.87, cluster 2 > cluster 3[a]
Range of state	3.80 ± 0.38	3.95 ± 0.68	3.85 ± 0.61	NS
Regulation of state	4.28 ± 0.93	4.96 ± 0.97	4.36 ± 0.88	NS

NS indicates not significant.

[a] $P < .05$.

TABLE 2 Emotional Regulation, Cognitive Development, and Symbolic and Executive Competences in State Transition Cluster Groups in First 5 Years of Life

	High Arousal (Cluster 1) ($N = 47$)	Organized Sleep-Wake (Cluster 2) ($N = 38$)	Disorganized Sleep (Cluster 3) ($N = 58$)	χ^2/U
Negative emotionality score at 3 and 6 mo, mean ± SD	1.39 ± 0.70	1.11 ± 0.27	1.56 ± 0.58	14.37, clusters 3 and 1 > cluster 2[a]
MDI, mean ± SD				
6 mo	92.12 ± 8.27	95.93 ± 6.99	92.48 ± 8.60	NS
12 mo	83.93 ± 11.37	91.03 ± 6.70	85.52 ± 10.06	10.26, cluster 2 > clusters 1 and 3[b]
24 mo	90.86 ± 14.50	120.70 ± 11.61	91.70 ± 12.94	16.33, cluster 2 > clusters 1 and 3[a]
PDI, mean ± SD				
6 mo	83.23 ± 11.36	89.62 ± 18.83	81.00 ± 12.76	6.17, cluster 2 > cluster 3[c]
12 mo	90.08 ± 11.92	87.84 ± 12.32	87.07 ± 11.06	NS
24 mo	88.06 ± 10.10	87.58 ± 8.63	87.14 ± 10.37	NS
Executive function score at 5 y, mean ± SD	96.23 ± 10.73	102.96 ± 9.85	94.27 ± 13.63	8.96, cluster 2 > clusters 1 and 3[c]
Symbolic play score at 5 y, mean ± SD	2.04 ± 1.00	2.75 ± 0.92	2.22 ± 0.92	14.37, cluster 2 > clusters 1 and 3[a]
Verbal IQ at 5 y, mean ± SD	94.80 ± 22.43	110.29 ± 11.26	95.83 ± 16.24	9.86, cluster 2 > clusters 1 and 3[b]

NS indicates not significant.

[a] $P \leq .001$.

[b] $P \leq .01$.

[c] $P < .05$.

second frames.[47–49] Symbolic competence was calculated on the basis of the proportion of complex symbolic episodes, denoting recreated scenarios from several hierarchically organized, imaginary elements.

Statistical Analyses

Because the distributions of several developmental outcome measures did not show equal variance across groups, a nonparametric approach to data analysis was used. Group differences in developmental outcomes at each age were tested with Kruskal-Wallis tests, followed by posthoc Mann-Whitney tests. Pearson correlations examined the associations between variables across the first 5 years.

RESULTS

Neonatal Stage

No differences in infant birth weight, GA, medical risk, or male/female ratio were found between the 3 state transition cluster groups (Table 1). However, Kruskal-Wallis tests showed differences in the distributions of quiet sleep ($\chi^2 = 6.08$; $P = .048$) and active sleep ($\chi^2 = 7.19$; $P = .027$). Posthoc Mann-Whitney tests showed no differences between cluster 1 and cluster 2, but differences were found between cluster 2 and cluster 3 in quiet sleep ($U = 368.0$; $P = .017$; area under the curve [AUC]: 0.18) and active sleep ($U = 366.0$; $P = .016$; AUC: 0.18). Similarly, differences were found between cluster 1 and cluster 3 in active sleep ($U = 532.5$; $P = .034$; AUC: 0.18).

Differences in the Neonatal Behavior Assessment Scale factors (orientation, range of state, and regulation of state) were tested with Kruskal-Wallis tests, and differences were found in orientation ($\chi^2 = 5.91$; $P = .05$). Posthoc tests showed differences between cluster 2 and cluster 3 ($U = 69.5$; $P = .012$; AUC: 0.03), which indicated that infants in the organized sleep-wake cluster showed better orientation already at the newborn stage.

Infants' Negative Emotionality

Kruskal-Wallis tests revealed differences in infant negative emotionality scores at 3 and 6 months (Table 2). Posthoc tests showed that infants in cluster 2 expressed less negative emotionality, compared with infants in cluster 1 ($U = 69.5$; $P = .012$; AUC: 0.03) and infants in cluster 3 ($U = 385.0$; $P = .0001$; AUC: 0.19), during interactions with their mothers and fathers. Marginally significant differences emerged between cluster 1 and cluster 3 ($U = 732.5$; $P = .07$; AUC: 0.26), with infants in cluster 3 expressing more negative emotionality than those in cluster 1.

Cognitive Development Across Infancy

Results of the analyses assessing group differences in infants' MDI scores at 6, 12, and 24 months showed no group differences at 6 months but significant differences at 12 and 24 months (Table 2). Posthoc tests showed that, at 12 months, infants in cluster 2 scored higher than infants in cluster 1 ($U = 449.5$; $P = .002$; AUC: 0.18) and infants in cluster 3 ($U = 598.5$; $P = .01$; AUC: 0.25). Similarly, at 24 months, infants in cluster 2 showed higher MDI scores than did infants in cluster 1 ($U = 362.5$; $P = .001$; AUC: 0.20) and infants in cluster 3 ($U = 412.5$; $P = .001$; AUC: 0.20).

Similar analyses conducted with children's PDI scores at 6, 12, and 24 months showed group differences only at 6 months and not at 12 and 24 months (Table 2). No differences were found in the motor development of infants in cluster 1 and cluster 2, but differences were found in PDI scores at 6 months between cluster 2 and cluster 3 ($U = 625.5$; $P = .014$; AUC: 0.31).

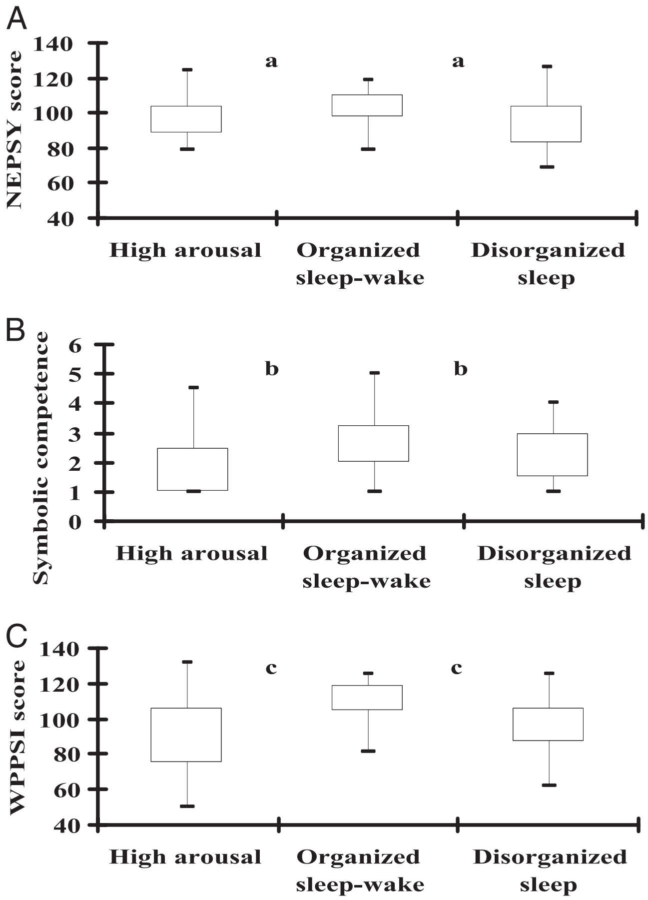

FIGURE 2

Developmental outcomes at 5 years according to state transition clusters in the neonatal period. Infants characterized by organized sleep-wake transitions (cluster 2) showed better developmental outcomes at 5 years. A, Executive functioning; B, symbolic competence; C, verbal IQ. Boxes represent lower and upper quartiles (Q1 and Q3) error bars represent minimum and maximum values. NEPSY indicates Developmental Neuropsychological Assessment test; WPPSI, Wechsler Preschool and Primary Scale of Intelligence. Infants characterized by organized sleep-wake transitions showed significantly better executive functioning (a), symbolic play (b), and verbal IQ (c) capabilities at 5 years.

Executive Functions, Symbolic Competence, and Verbal IQ at 5 Years

Group differences were found in executive functions, verbal IQ scores, and symbolic development at 5 years (Table 2 and Fig 2). Posthoc comparisons revealed no differences between children in cluster 1 and those in cluster 3. However, children in cluster 2 scored better than did those in cluster 1 with respect to executive function ($U = 300.0$; $P = .014$; AUC: 0.16), verbal IQ ($U = 262.5$; $P = .003$; AUC: 0.14), and symbolic competence ($U = 308.0$; $P = .004$; AUC: 0.17). Similarly, children in cluster 2 showed higher levels of performance than did those in cluster 3 with respect to executive function ($U = 362.5$; $P = .006$; AUC: 0.18), verbal IQ ($U = 275.5$; $P = .004$; AUC: 0.13), and symbolic competence ($U = 427.0$; $P = .021$; AUC: 0.21).

Bivariate Correlations Between Study Variables

Table 3 presents the intercorrelation matrix for all variables related to developmental follow-up evaluations. The low/modest correlations between variables suggest some interrelatedness between measures but indicate that the developmental outcomes tested here represent a variety of skills that do not load on a single factor. Finally, because the proportions of states showed differences between groups, we examined correlations between state distributions and outcome measures. The proportions of cry states were correlated with higher PDI scores at 6 months ($r = 0.18$; $P < .05$) and with greater negative emotionality in infancy ($r = 0.16$; $P < .05$), but no associations were found with 5-year measures. These findings indicate that, although state distributions dif-

TABLE 3 Bivariate Correlations Between Outcome Variables

	r							
	MDI at 6 mo	MDI at 12 mo	MDI at 24 mo	PDI at 6 mo	PDI at 12 mo	PDI at 24 mo	Executive Function Score at 5 y	Symbolic Play Score at 5 y
Negative emotionality score at 3 and 6 mo	−0.01	0.05	−0.05	0.00	−0.11	−0.01	−0.02	−0.14
MDI at 6 mo	—	0.42^a	0.29^a	0.55^a	0.23^a	0.21^b	0.06	0.85
MDI at 12 mo	—	—	0.31^a	0.31^a	0.41^a	0.22^b	0.19	0.17
MDI at 24 mo	—	—	—	0.19^b	0.25^a	0.33^a	0.32^a	0.24^b
PDI at 6 mo	—	—	—	—	0.29^a	0.10	0.05	0.09
PDI at 12 mo	—	—	—	—	—	0.39^a	−0.08	0.11
PDI at 24 mo	—	—	—	—	—	—	0.12	0.08
Executive function score at 5 y	—	—	—	—	—	—	—	0.27^a

^{a} $P \leq .01$.

^{b} $P < .05$.

fered among groups, they were not the defining neonatal markers that predicted developmental trajectories; the natures of the transitions between sleep and wake states were more powerful in detecting infants at greater or lesser risk. We also examined whether the mean durations of each state (ie, "bouts") were related to outcomes. No significant correlations between the durations of states and any outcome were found. Similarly, no group differences were found in the durations of any state.

DISCUSSION

Neonatal states are neurobehavioral constellations that index central nervous system maturity, health, and adaptation. The present study used a new approach to examine state organization, by focusing on how infants transition from sleep to wakefulness and from states of high and low arousal. The study also is the first to assess long-term associations with neonatal sleep across multiple domains. Results indicated that infants who shifted more smoothly between quiet sleep and wake states showed a more-mature neurodevelopmental profile, were better able to regulate negative emotions, and exhibited better cognitive and symbolic development, independent of birth weight, GA, and severity of medical course. Furthermore, the patterns of transitions between states, rather than the proportions or durations of each state, differentiated infants at higher and lower risk. Because the typical mode of an individual infant's state transitions can be assessed by medical and nursing staff members after brief training, these findings may provide a useful clinical tool in the neonatal period for identification of premature infants whose development may follow a better or worse course. Our observations are of particular value because the study population excluded infants who are typically considered to be at high medical risk (eg, with grade III/IV intraventricular hemorrhage or asphyxia) and those growing in high-risk contexts (eg, with single mothers or poverty). To date, there are nearly no valid indicators that can predict developmental outcomes among premature neonates born at relatively low risk, and the present findings are thus of special clinical importance. In particular, the results showing that the typologic features of sleep-wake transitions bear important consequences for later development may lead to the formation and implementation of interventions that focus on improving sleep organization in the neonatal period.

Three types of sleep-wake transition patterns emerged from the mathematical clustering of the sleep-state transition probabilities. Infants in the high-arousal transitions group tended to shift between a highly aroused sleep state (active sleep) and a highly aroused wake state (cry). Although those infants also showed transitions involving wake and quiet sleep states, most of their transitions included shifts to and from epochs of high arousal. Such shifts do not allow the fragile premature infant complete rest, which is required for growth, or uninterrupted alertness, which is required for early sensory learning and social contact. The maturation of the biological clock depends on the consolidation of clear cycles of activity and rest,[12] and infants in the organized sleep-wake transitions group seemed to show the most robust maturation of the biological clock.

The group that showed the poorest outcomes, cluster 3, included infants who transitioned mainly within sleep states. Those infants had few opportunities to reach the 2 optimal poles of the arousal continuum, quiet sleep and wakefulness, but also showed quick cycling between short epochs of high (active sleep) and low (quiet sleep) arousal. These shifts are associated with quick changes in brain activity accompanied by large metabolic expenditures, which are detrimental to the fragile premature brain[50]; therefore, such nonmodulated transitions between arousal states may impede neurobehavioral maturation. Interestingly, this group also showed especially low levels of performance on the orientation cluster of the Neonatal Behavior Assessment Scale. Possibly the quick shifts between high and low arousal decreased the newborn's capacity to orient to the environment in a regulated manner, and these early difficulties might have restricted the development of cognitive and social competences across early childhood.

Infants who showed more-organized transitions between sleep and wakefulness also exhibited greater verbal skills, greater symbolic competence, and better executive functions at 5 years. Interestingly, differences in cognitive functioning between groups emerged only after the first year of life and were observed at 12 and 24 months and in the 3 aspects of cognitive development at 5 years. These findings are consistent with longitudinal studies showing that differences related to birth conditions may become more apparent during the preschool period.[51] Moreover, cognitive development during the preschool years, particularly the set of skills grouped under "executive functions," depends on maturation of the prefrontal cortex.[52] Prefrontal maturation, which is known to depend on the environment, may reflect the associations between brain maturation and sleep organization in the neonatal period.[53] The parent-child relationship is of critical importance in the pathway leading from neonatal sleep to later outcomes, and it also is possible that infants in the group with more-regulated sleep elicited better parenting and had more opportunities for sensitive parental investment.

Although state organization has long been considered to provide the foundation for the development of children's capacities for attention, orientation to the world, and emotional regulation,[11–13,29] very little research has examined the developmental outcomes of individual variability in neonatal sleep organization. The present results demonstrated that such outcomes were related not to the distribution of states or the mean duration of each state but to the nature of the transitions between sleep and wakefulness. Similar to findings for the autonomic nervous system,[54] it seems that the way in which physiologic systems cycle between states of activity and rest and are able to accomplish the cycling between polarized ends in a rhythmic organized manner during the period when the systems are still in an immature stage may serve as an important indicator of the systems' innate coherence and potential for future growth.

Future research is required to examine birth-related risks that may shape long-term trajectories. Because most studies focused on cognitive testing or parental self-reports, future research should include observed measures of parenting, emotionality, or social relationships, to broaden the scope of skills assessed in relation to birth-related conditions. Because the parent-child relationship was not examined here, future research is needed to assess the independent and combined contributions of early sleep and parenting to children's emotional, cognitive, and symbolic development. It also is important to assess whether specific aspects of parenting, such as parent-child verbal communications, may moderate the effects of neonatal sleep on children's cognitive and symbolic growth. The findings indicated that infants in the high-arousal transitions group showed the highest level of negative emotionality, which might have interfered with the development of parenting and led to less parent-child communication and consequently lower levels of cognitive development, and this hypothesis should be tested. Finally, because we did not examine the distributions of sleep-wake transitions for term infants, future research is required to assess the links between state transitions and children's cognitive, social, and emotional dysfunctions in the general population. Such research is especially needed to devise specific parenting-related interventions that can improve the cognitive and emotional development of premature infants found to be at greater risk. We showed previously that maternal-infant skin-to-skin contact improves sleep patterns for premature neonates,[16] and additional research may specify parenting practices that can be applied throughout infancy, can assist infants in developing better sleep organization, and can lead to better outcomes.

Limitations of the study include the lack of parent-child interaction data for assessment of the impact of parenting in moderating the links between neonatal sleep and outcomes. In addition, we included only middle-class intact families, and generalization of the findings to children growing in more-disorganized environments, which provide less regulated context for growth, needs to be assessed. The temporal organization of sleep as a potential marker of developmental risk requires further research for evaluation of physiologic, behavioral, brain, and mental aspects in healthy newborns, as well as among those born under conditions of biological and environmental risk.

REFERENCES

1. Caravale B, Tozzi C, Albino G, Vicari S. Cognitive development in low risk preterm infants at 3–4 years of life. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(6):F474–F479
2. Ross G, Lipper EG, Auld PAM. Educational status and school-related abilities of very low birth weight premature children. *Pediatrics*. 1991;88(6):1125–1134
3. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA*. 2002;288(6):728–737
4. Crnic KA, Ragozin AS, Greenberg MT, Robinson NM, Basham RB. Social interaction and developmental competence of preterm and full-term infants during the first year of life. *Child Dev*. 1983;54(5):1199–1210
5. Anderson PJ, Doyle LW. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics*. 2004;114(1):50–57
6. Bayless S, Stevenson J. Executive functions in school-age children born very prematurely. *Early Hum Dev*. 2007;83(4):247–254
7. Marlow N, Hennessy EM, Bracewell MA, Wolke D; EPICure Study Group. Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics*. 2007;120(4):793–804
8. Victorian Infant Collaborative Study Group. Eight-year outcome in infants with birth weight of 500 to 999 grams: continuing regional study of 1979 and 1980 births. *J Pediatr*. 1991;118(5):761–767
9. Victorian Infant Collaborative Study Group. Neurosensory outcome at 5 years and extremely low birthweight. *Arch Dis Child Fetal Neonatal Ed*. 1995;73(3):F143–F146
10. Halpern LF, MacLean WE, Baumeister AA. Infant sleep-wake characteristics: relation to neurological status and the prediction of developmental outcome. *Dev Rev*. 1995;15(3):255–291
11. Thoman EB. A biological perspective and a behavioral model for assessment of premature infants. In: Bond LA, Joffee JM, eds. *Primary Prevention of Psychopathology*. Hanover, NH: University Press of New England; 1982:159–179
12. Levitt P. Structural and functional maturation of the developing primate brain. *J Pediatr*. 2003;143(4 suppl):S35–S45
13. Holditch-Davis D, Thoman EB. Behavioral states of premature infants: implications for neural and behavioral development. *Dev Psychobiol*. 1987;20(1):25–38

14. Feldman R. From biological rhythms to social rhythms: physiological precursors of mother-infant synchrony. *Dev Psychol*. 2006;42(1):175–188
15. Mirmiran M, Lunshof S. Perinatal development of human circadian rhythms. *Prog Brain Res*. 1996;111:217–226
16. Feldman R, Weller A, Sirota L, Eidelman AI. Skin-to-skin contact (kangaroo care) promotes self-regulation in premature infants: sleep-wake cyclicity, arousal modulation, and sustained exploration. *Dev Psychol*. 2002;38(2):194–207
17. Feldman R, Eidelman AI. Skin-to-skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Dev Med Child Neurol*. 2003;45(4):274–281
18. Thoman EB, Hammond K, Affleck G, DeSilva HN. The breathing bear with preterm infants: effects on sleep, respiration, and affect. *Infant Mental Health J*. 1995;16(3):160–168
19. Doussard-Rossevelt J, Porges SW, McClenny BD. Behavioral sleep states in very low birth weight preterm neonates: relation to neonatal health and vagal maturation. *J Pediatr Psychol*. 1996;21(6):785–802
20. Anders TF, Keener MA, Kraemer H. Sleep-wake state organization, neonatal assessment and development in premature infants during the first year of life. *Sleep*. 1985;8(3):193–206
21. Borghese IF, Minard KL, Thoman EB. Sleep rhythmicity in premature infants: implications for developmental status. *Sleep*. 1995;18(7):523–530
22. Feldman R, Eidelman AI. Neonatal state organization, neuromaturation, mother-infant interaction, and cognitive development in small-for-gestational-age premature infants. *Pediatrics*. 2006;118(3). Available at: www.pediatrics.org/cgi/content/full/118/3/e869
23. Beckwith L, Parmelee AH. EEG patterns of preterm infants, home environment and later IQ. *Child Dev*. 1986;57(3):777–789
24. Gertner S, Greenbaum CW, Sadeh A, Dolfin Z, Sirota L, Ben-Nun Y. Sleep-wake patterns in preterm infants and 6 month's home environment: implications for early cognitive development. *Early Hum Dev*. 2002;68(2):93–102
25. Arditi-Babchuk H, Feldman R, Eidelman AI. Rapid eye movement (REM) in premature neonates and developmental outcome at 6 months. *Infant Behav Dev*. 2009;32(1):27–32
26. Ednick M, Cohen AP, McPhail GL, Beebe D, Simakajornboon N, Amin RS. A review of the effects of sleep during the first year of life on cognitive, psychomotor, and temperament development. *Sleep*. 2009;32(11):1449–1458
27. Pearl PL, Efron L, Stein MA. Children, sleep, and behavior: a complex association [in Italian]. *Minerva Pediatr*. 2002;54(2):79–91
28. Sadeh A, Gruber R, Raviv A. The effects of sleep restriction and extension on school-age children: what a difference an hour makes. *Child Dev*. 2003;74(2):444–455
29. Dahl RE. The regulation of sleep and arousal: development and psychopathology. *Dev Psychopathol*. 1996;8(1):3–27
30. Feldman R, Eidelman AI, Sirota L, Weller A. Comparison of skin-to-skin (kangaroo) and traditional care: parenting outcomes and preterm infant development. *Pediatrics*. 2002;110(1):16–26
31. Sadeh A, Gruber R, Raviv A. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Dev*. 2003;73(2):405–417
32. Holditch-Davis D, Scher M, Schwartz T, Hudson-Barr D. Sleeping and waking state development in preterm infants. *Early Hum Dev*. 2004;80(1):43–64
33. Harlap S, Davies AM, Grover NB, Prywes R. The Jerusalem Perinatal Study: the first decade (1964–1973). *Isr J Med Sci*. 1977;13(11):1073–1091
34. International Neonatal Network. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet*. 1993;342(8865):193–198
35. Holditch-Davis D. The development of sleeping and waking states in high-risk preterm infants. *Infant Behav Dev*. 1990;13(4):513–531
36. Brazelton TB. *The Neonatal Behavioral Assessment Scale*. Philadelphia, PA: Lippincott; 1973
37. Lester BM. Data analysis and prediction. In: Brazelton TB, ed. *Neonatal Behavioral Assessment Scale*. 2nd ed. London, United Kingdom: Spastic International Medical Publications; 1984
38. Feldman R. *Coding Interactive Behavior (CIB) Manual*. Ramat Gan, Israel: Bar-Ilan University; 1998
39. Feldman R, Greenbaum CW, Mayes LC, Erlich HS. Change in mother-infant interactive behavior: relations to change in the mother, the infant, and the social context. *Infant Behav Dev*. 1997;20(2):153–165
40. Feldman R, Keren M, Gross-Rozval O, Tyano S. Mother-child touch patterns in infant feeding disorders: relation to maternal, child, and environmental factors. *J Am Acad Child Adolesc Psychiatry*. 2004;43(9):1089–1097
41. Feldman R, Klein PS. Toddlers' self-regulated compliance with mother, caregiver, and father: implications for theories of socialization. *Dev Psychol*. 2003;39(4):680–692
42. Feldman R, Masalha S, Nadam R. Cultural perspective on work and family: dual-earner Israeli-Jewish and Arab families at the transition to parenthood. *J Fam Psychol*. 2001;15(3):492–509
43. Feldman R, Weller A, Sirota L, Eidelman AI. Testing a family intervention hypothesis: the contribution of mother-infant skin-to-skin contact (kangaroo care) to family interaction, proximity, and touch. *J Fam Psychol*. 2003;17(1):94–107
44. Bayley N. *Bayley Scales of Infant Development: Administering and Scoring Manual*. 2nd ed. New York, NY: Psychological Corp; 1993
45. Wechsler D. *Manual for Wechsler Preschool and Primary Scale of Intelligence*. New York, NY: Psychological Corp; 1967
46. Korkman M, Kirk U, Kemp S. *NEPSY: A Developmental Neuropsychological Assessment*. San Antonio, TX: Psychological Corp; 1998
47. Feldman R, Greenbaum CW. Affect regulation and synchrony in mother-infant play as precursors to the development of symbolic competence. *Infant Mental Health J*. 1997;18(1):4–23
48. McCune L. A normative study of representational play at the transition to language. *Dev Psychol*. 1995;31(2):198–206
49. Tamis-LeMonda CS, Bornstein MH. Individual variation, correspondence, stability, and change in mother and toddler play. *Infant Behav Dev*. 1991;14(2):143–162
50. Madsen PL, Vorstrup S. Cerebral blood flow and metabolism during sleep. *Cerebrovasc Brain Metab Rev*. 1991;3(4):281–296
51. Feldman R, Eidelman AI. Biological and environmental initial conditions shape the trajectories of cognitive and social-emotional development across the first years of life. *Dev Sci*. 2009;12(1):194–200
52. Zelazo PD, Carlson SM, Kesek A. The development of executive function in childhood. In: Nelson C, Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience*. Cambridge, MA: MIT Press; 2008:553–574
53. Jones BE. From waking to sleeping: neuronal and chemical substrates. *Trends Pharmacol Sci*. 2005;26(11):578–586
54. Porges SW. Social engagement and attachment: a phylogenetic perspective: roots of mental illness in children. *Ann N Y Acad Sci*. 2003;1008:31–47

Sleep-Wake Transitions in Premature Neonates Predict Early Development

Omri Weisman, Reuma Magori-Cohen, Yoram Louzoun, Arthur I. Eidelman and Ruth Feldman

Pediatrics 2011;128;706; originally published online September 12, 2011;
DOI: 10.1542/peds.2011-0047

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/128/4/706.full.html
References	This article cites 45 articles, 8 of which can be accessed free at: http://pediatrics.aappublications.org/content/128/4/706.full.html#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Premature & Newborn** http://pediatrics.aappublications.org/cgi/collection/premature_and_newborn
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://pediatrics.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://pediatrics.aappublications.org/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2011 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from pediatrics.aappublications.org at YALE MEDICAL LIBRARY on January 5, 2012