



## Rapid eye movement (REM) in premature neonates and developmental outcome at 6 months

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### ABSTRACT

Different aspects of early sleep organization have been associated with subsequent development in premature infants. The aim of the present study was to assess the relations between rapid eye movement (REM) activity in premature neonates and infants' developmental outcomes at 6 months. Participants were 81 premature infants (47 males). Sleep–wake states and REM were observed across 4 consecutive evening hours (7–11PM) in 10-s frames when infants were between 32 and 36 weeks post-menstrual age. Developmental outcome was assessed at 6 months with the mental development index (MDI) of the Bayley II. Infants with low-REM activity spent more time in less growth-promoting states, including crying and unfocused alert states in the neonatal period and had lower MDI scores at 6 months corrected age compared to infants with high-REM. Differences between the high- and low-REM groups were independent of neonatal medical risk. Low-REM activity may serve as an indicator of developmental risk among premature neonates.

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### 1. Introduction

The organization of sleep in infancy, particularly among premature infants, provides an index of neurological maturation and CNS intactness. Several studies indicated that during the first weeks of life, quiet sleep increases while active sleep decreases (Holditch-Davis, 1990; Holditch-Davis & Edwards, 1998; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Ingersoll & Thoman, 1999). These developmental changes in the balance of quiet to active sleep have been associated with the infant's ultimate development. For instance, all-night recording of infant sleep states at 2, 4, 8, 20, 24, 36 and 52 weeks showed that progressive lengthening of quiet sleep periods was related to better mental performance at 6 months, and the stability of sustained sleep (long periods of uninterrupted sleep) predicted better mental performance at 12 months (Andres, Keener, & Kraemer, 1985).

Premature infants are at a higher risk for the development of cognitive delays and disabilities (Caravale, Tozzi, Albino, & Vicari, 2005) and thus, behavioral measures that can be applied in the neonatal period and can detect neurophysiological processes that predict later development are of clinical importance. The organization of quiet and active sleep states may provide one such behavioral measure. Previous reports of sleep states over three consecutive 24-h periods at 36 weeks post-menstrual age showed that a shorter mean duration of active sleep and a shorter mean duration of the active–quiet sleep cycle were related to better cognitive development at 6 months (Borghese, Minard, & Thoman, 1995). Similarly, weekly

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observations of pre-term infants' sleep patterns assessed over 4 h revealed that infants who showed more rapid decrease in active sleep had higher intelligence and better language and fine motor skills at 3 years (Holditch-Davis, Belyea, & Edwards, 2005).

Active sleep not only decreases with the infant's maturation but also becomes more organized. Typically, active sleep with rapid eye movements (REM) increases (Holditch-Davis, 1990) while active sleep without REM decreases (Holditch-Davis & Edwards, 1998). More active sleep without REM characterizes infant populations with developmental delays, and was found, for instance, among infants with intrauterine growth retardation (Watt & Strongman, 1985). In contrast, greater REM activity is related to better developmental outcome. Among infants with developmental disabilities of unknown etiology, higher percentages of REM out of the total sleep time was related to better motor, exploratory, social, eating, and intellectual outcomes (Shibagaki, Sawata, & Tachibana, 2004).

Although active sleep with REM is considered to reflect a more organized and mature CNS functioning as compared to active sleep with no REM (Holditch-Davis, 1990; Holditch-Davis & Edwards, 1998) the relations between REM sleep and developmental outcome in premature infants has not been fully addressed. REM sleep is thought to activate the same brain circuits as those required for learning and memory (Dujardin, Guerrien, & Leconte, 1990) and thus, better understanding of the developmental sequelae of REM sleep may be informative to specifying the mechanisms underlying the cognitive delays common in premature infants (Caravale et al., 2005). Moreover, analysis of neonatal REM during active sleep may serve as an early indicator for immature neurophysiological processes and may help detect infants who are at higher risk for non-optimal growth. Previous findings have shown that REM levels are related to cognitive functioning mainly in populations in which REM levels are low, for instance, in individuals with mental retardation (Castaldo, 1969; Jouvett & Petre-Quadens, 1966). In this study, REM was measured at 32–36 weeks post-conceptual age. At these stages REM levels are still low and much variability can be observed among infants. As such, it was expected that individual differences in REM would be most reflective of CNS functioning and maturation at these early stages. Cognitive development was assessed at 6 months, as this is the earliest stage in which Bayley MDI score are stable across time and have shown to predict cognitive and social-emotional development across infancy and early childhood (Feldman & Eidelman, 2005, Feldman & Eidelman, 2008). It was hypothesized that infants with higher REM during the neonatal period would show better developmental outcome at 6 months. It was also expected that infants with higher REM levels would have more organized sleep–wake patterns in the neonatal period and thus, the distribution of sleep–wake states was assessed. Furthermore, we expected infants with greater REM activity to show lower frequency of less growth-promoting states including transitory states (Feldman, Weller, Sirota, & Eidelman, 2002) and cry (Ludington-Hoe, Cong, & Hashemi, 2002).

## 2. Methods

### 2.1. Participants

Eighty-one low birth-weight premature infants participated. The sample was drawn from a consecutive birth sample collected between March 1996 and December 1999 at the Neonatal Intensive Care Unit of Shaare Zedek Medical Center, a tertiary-care medical hospital in Jerusalem, Israel. To eliminate potential confounders, only mothers who were above 20 years, married to the infant's father, and who completed at least 12 years of schooling were included. The sample was considered to be middle class by Israeli standards (Harlap et al., 1977). Mothers were approached to participate in a developmental follow-up and among those approached 8 mothers declined participation, citing time constraints as reason. Those mothers and infants did not differ on demographic or infant medical variables from the participating families. In this study, infants who had state observation at 32–36 weeks and met medical inclusion criteria were included. Exclusion criteria were grade 3–4 intraventricular hemorrhage, periventricular leucomalacia, perinatal asphyxia, metabolic or genetic disease, central nervous system infection, and an abnormal neurological examination before discharge. The sample included 47 males and 34 females. Mean birth weight was 1463.48 (S.D. = 446.44, range 520–2830), and mean post-menstrual age was 30.97 weeks (S.D. = 2.41, range 26–35). Mean CRIB score was 1.8 (S.D. = 2.48, range 0–11). Infants were tested as part of a longitudinal follow-up program of infant development. The study was approved by the Institutional Review Board and informed consent was obtained from one or both parents.

### 2.2. Procedures and measures

#### 2.2.1. State observation and coding

Trained coders observed infant's state during four consecutive evening hours (7–11 PM). During these hours, per departmental routines, there were no invasive medical procedures or oral or gavage feeding conducted in the NICU, enabling a relatively smooth observation of infant state. State was observed and entered into a computerized program in 10-s epochs. Observations took place at a mean post-menstrual age of 33.76 weeks (S.D. = 1.35, range 32–36), at a mean of 21.14 days chronological age (S.D. = 15.52, range 1–72). State observation lasted for 4 h. In cases of unexpected interruptions, if the observation included 3 h or more the data was sufficient to detect sleep–wake cyclicity as the sleep–wake cycle in neonates lasts between 60 and 70 min (Stern, Parmelee, & Harris, 1973), and this occurred in 18% of the cases. If the observation included less than 3 h, it was terminated and resumed when the infant returned to a calm state, and this occurred in 7% of the cases. Coders were trained to reliability using observations on infants and coding from a training tape that included

infants at different GA and medical risk in real time, using a hidden beeper that beeped every 10 s. When 85% reliability was reached on the tape, coders were trained in the nursery. Reliability of each coder (8 students of psychology) was measured against the chief neonatologist. Reliability on 12 infants at different ages averaged 92%, kappa = .85 and reliability remained the same during the last hour of the observation.

States and REM sleep coding were modeled after Brazelton (1973) and Holditch-Davis (1990) and were defined as follows:

- (1) *Quiet sleep*: infant's eyes are closed, breathing is regular, and motor activity is minimal.
- (2) *Active sleep*: infant's eyes are closed, respiration is irregular and motor activity and rapid eye movement occur sporadically.
- (3) *Sleep-wake transition*: eyes are typically closed but may open occasionally, motor activity is typical, and behaviors of both sleep and wakefulness are observed.
- (4) *Unfocused wakefulness*: eyes are typically open but may occasionally close, and motor activity is typically high.
- (5) *Alert wakefulness*: eyes are open and scanning, and motor activity is medium-range.
- (6) *Fuss/cry*: eyes are typically open, motor activity is typical, and the infant emits clear fuss vocalization or full cry.

For each 10-s period of active sleep state one of the following codes were applied:

- (1) *No REM*: no rapid eye movements (REM) were observed during an entire 10-s epoch of active sleep.
- (2) *REM*: REM with small excursion lasting 1–8 s were observed, or REM with large excursions lasting less than half an epoch of active sleep.
- (3) *REM storm*: continuous small REMs for the entire epoch, or large REMs for more than half an epoch of active sleep.

Reliability for REM activity was conducted for 12 infants and averaged 89% (kappa = .80).

Sleep-wake and REM states were measured as percentages of the global observations. In addition, infants were divided to two groups of high- and low-rapid eye movement (REM) according to the median of REM activity (4.79% of the observation time).

### 2.2.2. Infant medical risk

Infants' medical risk was measured with the clinical risk index for babies (CRIB) (International Neonatal Network, 1993). The CRIB is an objective quantitative measure of neonatal risk for infants born prematurely that evaluates birth weight, gestational age, minimum and maximum fraction of inspired oxygen, minimum base excess during the first 12 h, and the presence of congenital malformations. Scores are then summed to create the total CRIB score and higher scores represent a greater risk. CRIB scores ranged from 0 to 9 and the means for the two groups are presented in Table 1. Validation for using the CRIB for developmental research is indicated by the correlations between the CRIB scores and infants' performance on the Neonatal Behavior Assessment Scale (Brazelton, 1973) upon discharge, indicating poorer neurobehavioral maturation, and the concordance between groups created by the CRIB and by the Neuro-Behavioral Risk Score (NBRS Brazyl, Eckerman, Oehler, Goldstein, & O'Rand, 1991), a second comprehensive index of medical risk.

### 2.2.3. Cognitive development

Infants were tested with the Bayley scales of infant development II (Bayley, 1993) at 6 months of age by trained and blinded psychologists. Infant age at testing was corrected to prematurity (40 weeks gestation).

**Table 1**  
Medical and demographic information in the two REM groups.

|                                     | Low-REM M, S.D. | High-REM M, S.D. | F/ $\chi^2$ |
|-------------------------------------|-----------------|------------------|-------------|
| Birth weight (g)                    | 1417.16, 468.91 | 1528.64, 449.95  | NS          |
| Post-menstrual age at birth (weeks) | 31.03, 2.59     | 31.07, 2.34      | NS          |
| Medical risk (CRIB score)           | 2.50, 3.14      | 1.21, 1.37       | 5.35*       |
| RDS                                 | 19              | 18               | NS          |
| BPD                                 | 5               | 4                | NS          |
| Ventilation (days)                  | 3.40, 6.41      | 3.68, 8.24       | NS          |
| Chronological age (days)            | 20.76, 15.43    | 22.42, 17.20     | NS          |
| Mother age (years)                  | 27.43, 5.20     | 29.00, 6.08      | NS          |
| Mother education                    |                 |                  |             |
| High school/College/University      | 11/17/8         | 10/24/2          | NS          |
| Father age (years)                  | 30.13, 6.78     | 31.71, 6.57      | NS          |
| Father education                    |                 |                  |             |
| High school/College/University      | 13/10/13        | 19/7/8           | NS          |
| Males                               | 24              | 23               | NS          |
| No. of siblings                     | 2.63, 1.93      | 2.78, 2.13       | NS          |

\*  $p < .05$ .

**Table 2**  
States' distribution according to REM group.

|                  | Low-REM M, S.D. | High-REM M, S.D. | F(7, 71) |
|------------------|-----------------|------------------|----------|
| Quiet sleep (%)  | 32.48, 20.15    | 29.15, 15.33     | NS       |
| Active sleep (%) | 37.27, 19.64    | 54.29, 13.40     | NS       |
| Transition (%)   | 12.18, 18.35    | 7.96, 6.09       | NS       |
| Unfocused (%)    | 9.68, 7.26      | 5.56, 5.63       | 5.72*    |
| Fuss/cry (%)     | 4.54, 5.85      | 1.55, 1.76       | 5.40**   |
| Alert (%)        | 3.72, 7.76      | 1.49, 3.05       | 2.59†    |

\*  $p < .05$ .

\*\*  $p < .01$ .

†  $p < .10$ .

### 2.3. Statistical analysis

A multivariate analysis of variance with medical risk as a covariate (MANCOVA) was conducted to evaluate differences in state distribution between the high- and low-REM groups. An analysis of variance with medical risk as a covariate (ANCOVA) was conducted to evaluate differences in cognitive development at 6 months between the groups. Partial correlations controlling for medical risk were computed for the relations between REM measures and 6 months' cognitive development. Correlations were also computed for the relation between medical and demographic variables and 6 months' cognitive development. A hierarchical multiple regression model was used to predict infants' cognitive outcome at 6 months from medical and demographic variables and REM proportion.

## 3. Results

Medical and demographic information for the high- and low-REM groups is presented in Table 1. No difference was found between the groups in birth weight, post-menstrual age at birth, percentage of infants suffering from the respiratory distress syndrome (RDS) or chronic lung disease (bronchopulmonary dysplasia-BPD), duration of mechanical ventilation, chronological age at observation, mother age or education, father age or education, or number of siblings. However, a difference was found between the groups in medical risk. Infants with high-REM activity had lower medical risk score ( $M = 1.21$ ,  $S.D. = 1.37$ ) as compared to infants with low-REM ( $M = 2.50$ ,  $S.D. = 3.14$ ). In order to explore the effects of REM on state distribution and subsequent development, all the following analysis of variance were computed while controlling for medical risk.

Infants in the high-REM group had active sleep with REM for a mean of 11.78% of the observation time ( $S.D. = 8.35$ ) while infants in the low-REM group had active sleep with REM for a mean of 1.87% of the observation time ( $S.D. = 1.42$ ). An analysis of variance with medical risk as a covariate for group effect on REM storm proportions showed a significant difference between the groups  $F(2, 77) = 3.37$ ,  $p < .05$ . Infants in the high-REM group had REM storms for a mean of 1.05% ( $S.D. = 2.26$ ) of the observation time while infants in the low-REM group had REM storms for a mean of 0.12% ( $S.D. = 0.25$ ) of the observation time.

### 3.1. State distribution in the high- and low-REM groups

A multivariate analysis of variance with medical risk as a covariate for the effect of REM group on state distribution showed a main effect for group Wilks'  $F(d.f. = 6, 72) = 11.20$ ,  $p < .001$ . Means, standard deviations and  $F$  values of states distribution are presented in Table 2. As can be seen, infants in the high-REM group had lower proportions of fuss/cry and unfocused states, and somewhat lower proportions of alert wakefulness as compared to infants in the low-REM sleep group.

### 3.2. Predicting MDI at 6 months

An ANCOVA assessing the effect of group on infants' mental development index (MDI) at 6 months showed an effect for group on MDI  $F(2, 69) = 6.51$ ,  $p < .01$ . Infants in the high-REM group had a mean MDI of 95.25 ( $S.D. = 5.44$ ) at 6 months while infants in the low-REM group had a mean MDI of 91.80 ( $S.D. = 5.66$ ). Partial correlations controlling for medical risk score were found between REM and MDI,  $r(69) = .27$ ,  $p < .05$ . Higher REM proportions were related to higher MDI at 6 months. No partial correlations were found between active sleep with no REM,  $r(69) = .00$ ,  $p > .10$ , or between REM storms  $r(69) = .16$ ,  $p > .10$ , and MDI. Correlations were found between birth weight,  $r(72) = .28$ ,  $p < .05$ , post-menstrual age at birth,  $r(72) = .27$ ,  $p < .05$ , medical risk scores,  $r(71) = -.33$ ,  $p < .01$ , and MDI. No correlations were found between maternal education and MDI,  $r(65) = -.05$ ,  $p > .10$ , possibly because of the homogeneity of the sample in terms of socio-economic status.

A hierarchical multiple regression model was used to predict infants' cognitive outcome at 6 months. Predictors were entered in 4 blocks. In the first block, birth weight and post-menstrual age at birth were entered. In the second block, the infant's medical risk score was entered. In the third block maternal education was entered. Finally, after partialing out variance related to child medical risk and maternal education, REM level was entered in the fourth block. The regression

**Table 3**  
Prediction of MDI at 6 months.

|                    | $\beta$ | $R^2$ change | $F$ change | d.f.  |
|--------------------|---------|--------------|------------|-------|
| Birth weight       | .17     |              |            |       |
| Gestational age    | .07     | .09          | 3.38*      | 2, 62 |
| Medical risk       | -.12    | .02          | 1.71       | 3, 61 |
| Maternal education | .00     | .00          | .01        | 4, 60 |
| REM                | .29     | .08          | 5.96*      | 5, 59 |

$R^2$  total = .20,  $F(5, 59) = 3.02$ .

\*  $p < .05$ .

model is presented in Table 3. As seen, REM predicted infants' mental development at 6 months above and beyond birth weight and post-menstrual age at birth, medical risk, and maternal education. Higher REM proportions were related to better MDI at 6 months.

#### 4. Discussion

This study examined the relations between rapid eye movements (REM) during active sleep in premature neonates and cognitive development at 6 months. We found that increased REM activity was associated with more optimal development independent of the degree of infant medical risk. Infants with more REM had better cognitive outcome at 6 months and REM activity levels predicted better cognitive development above and beyond birth status and medical risk. These findings are consistent with those reported by Buhner, Grimmer, Metze, and Obladen (2000), who found that CRIB scores alone provided poor prediction of ultimate neurodevelopmental function.

Infants with greater REM activity showed more optimal state organization and spent less time in crying states and unfocused wakefulness as compared to infants with lower REM activity. As excessive crying may negatively impact the fragile premature infant's energy conservation and growth (Ludington-Hoe et al., 2002), reduced crying, in turn, may be developmentally beneficial. Moreover, premature infants with high levels of crying were found to score lower on the "habituation" and "regulation of state" clusters of the neonatal behavioral assessment scale (NBAS) (Ohgi, Gima, & Akiyama, 2006).

Infants with higher REM levels showed greater amounts of intense REM bursts, that is, REM storms; yet, no associations were found between REM storms and infants development. It is interesting in this context to note the developmental difference between REM storms observed during the pre-term period and those observed at later stages. In full-term 6 months old infants, higher REM storms rates were related to lower MDI scores at 12 months (Becker & Thoman, 1981). REM storms at this stage may result from immature inhibitory controls of the central nervous system and reflect a failure in the proper maturation of control systems. However, in the pre-term period, inhibitory systems are still immature, and thus REM storms may not reflect a developmental abnormality.

Our findings that neonatal REM activity in the pre-term infant predicts cognitive competencies at 6 months are consistent with findings from other age groups and populations. Less REM sleep was found in mentally retarded subjects as compared to typically developing controls (Jouvet & Petre-Quadens, 1966) and adolescents with mild retardation had more REM time and shorter REM latencies compared to those with severe retardation (Castaldo, 1969). Among individuals with mental retardation, greater REM activity was associated with higher intelligence in both adolescents and adults (Diomedi et al., 1999; Feinberg, Braun, & Shulman, 1969), even when mental retardation was functional and was not related to any organic dysfunction (Castaldo & Krynicki, 1973).

Processes of learning and memory are enhanced during REM sleep. For instance, an intensive learning period of senior college students during final examination periods resulted in an increase in the number of REMs and REM density (Carlyle & Lapp, 1991). The efficiency of learning a conversational second language was positively related to increases in the percentage of REM sleep from the pre-course to the course period (de-Koninck, Lorrian, Christ, Proulx, & Coulombe, 1989). Among infants, successful acquisition of a head-turning response was followed by an increase in REM time relative to baseline. In contrast, failure to learn a more complex response was not followed by increase in REM time (Paul & Dittrichova, 1974). In light of the finding that more optimal developmental outcome was found in premature infants showing higher REM levels, it is possible that REM sleep contributes to processes of learning and development in premature infants as well.

It should be noted that no videotaped recording was taken during the observation period. Thus, we cannot rule out the possibility that differences in REM levels between the groups stem from differences in nursing interventions of the medical staff. However, no difference was found between the groups in medical condition (BPD, respiratory distress syndrome or length of mechanical ventilation) and apparently, the low-REM group did not need greater nursing than the high-REM group.

Future studies aiming at the relations between REM and developmental risk among premature infants may examine whether REM is related to predictors of developmental outcome in premature infants. For example, among premature neonates, visual fixation time was related to information processing ability through childhood and youth (Sigman, Cohen, & Beckwith, 1991a; Sigman, Cohen, Beckwith, Asarnow, & Parnellee, 1991b). Examining the relation between REM activity and visual fixation may further illuminate the mechanisms underlying cognitive development in premature infants.

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