# Skin-to-skin contact (Kangaroo Care) accelerates autonomic and neurobehavioural maturation in preterm infants

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**The effects of mother–infant skin-to-skin contact (Kangaroo Care; KC) on autonomic functioning, state regulation, and neurobehavioural status was examined in 70 preterm infants, half of whom received KC over 24.31 days (SD 7.24) for a total of 29.76 hours (SD 12.86). Infants were matched for sex (19 males and 16 females in each group); birthweight (KC, 1229.95g [SD 320.21]; controls, 1232.17g [SD 322.15]); gestational age (GA) (KC, 30.28 weeks [SD 2.54]; controls, 30.19 weeks [SD 2.65]); medical risk; and family demographics. Vagal tone was calculated from 10 minutes of heart rate before KC and again at 37 weeks' GA. Infant state was observed in 10-second epochs during four consecutive hours before KC and again at 37 weeks' GA. Neurobehavioural status was assessed at 37 weeks' GA with the Neonatal Behavioral Assessment Scale (NBAS). Infants receiving KC showed a more rapid maturation of vagal tone between 32 and 37 weeks' GA ($p$=0.029). More rapid improvement in state organization was observed in KC infants, in terms of longer periods of quiet sleep ($p$=0.016) and alert wakefulness ($p$=0.013) and shorter periods of active sleep ($p$=0.023). Neurodevelopmental profile was more mature for KC infants, particularly habituation ($p$=0.032) and orientation ($p$=0.007). Results underscore the role of early skin-to-skin contact in the maturation of the autonomic and circadian systems in preterm infants.**

Newborn 'maturity' is a neurodevelopmental construct denoting an organized, smoothly functioning, and properly integrated neurophysiological and behavioural system. Specifically, newborn maturation implies the capacity to regulate internal state and to mobilize sufficient energy to orient to social and non-social stimuli (Brazelton 1990). Of the various indices of newborn maturation, the most frequently studied are vagal tone, state organization, and neurobehavioural status assessed with tests such as the Neonatal Behavioral Assessment Scale (NBAS; Brazelton 1973). Common to these indices is their utility in differentiating infants at various levels of medical risk (Colombo et al. 1989, Holditch-Davis 1990, Porges 1992) and their predictability of infants' later cognitive and social functioning (Thoman et al. 1981, Risholm-Mothander 1989, Doussard-Roosevelt et al. 1997).

One objective, clinically-relevant index for the integrity and maturity of the nervous system in preterm infants is cardiac vagal tone, which measures the effect of respiration on heart-rate variability as mediated by the parasympathetic system. Porges (1995, 1996) suggested that vagal tone is an index of the organization of the mammalian brainstem and its adaptive ability to differentially mobilize or save energy in response to external or internal stresses. Measures of heart rate variability and vagal tone have been correlated with the newborn infant's clinical status, gestational age (GA), respiratory distress, intrauterine growth rate, and cry pitch frequencies (Porter et al. 1988, van Ravenswaaij-Arts et al. 1991, Spassov et al. 1994). The vagal tone of preterm infants does not reach full maturity at term age and the rate of vagal tone maturation is related to postnatal weight gain and length of hospitalization (DiPietro and Porges 1991). The resting vagal tone at term age was found to predict infant development up to six years of age, although results of some studies should be interpreted with caution owing to non-randomization and small sample sizes (Fox and Porges 1985, Doussard-Roosevelt et al. 2001).

State regulation is another maturation index, which evolves in a predictable fashion during the last trimester of pregnancy and is frequently delayed in preterm infants developing in an extrauterine environment (Curzi-Dascalova et al. 1986, Shimada et al. 1999, Mirmiran and Ariagno 2000). Preterm infants spend shorter periods in alert wake and quiet sleep states, spend longer periods in active sleep states, and show less organized sleep–wake rhythmicity. The shorter the gestation and the more severe the medical condition at birth, the greater are the disturbances in state organization and the poorer the rate of maturation (Holditch-Davis and Thoman 1986, Ingersoll and Thoman 1999). The degree of state organization at term age has also been shown to predict neurobehavioural, cognitive, and motor development in infancy and early childhood (Anders et al. 1985, Beckwith and Parmelee 1986).

Neurodevelopmental status, as assessed by the NBAS, is among the central tools for the evaluation of functioning of newborn infants. Of the NBAS clusters, disturbances in orientation are most associated with a variety of risk signals. Poorer orientation is correlated with higher basal and responsivity cortisol levels (Spangler and Scheubeck 1993), negative emotionality (Auerbach et al. 1999), prenatal exposure to cocaine (Held et al. 1999), and newborn macrosomy (Pressler and Hepworth 1997). Disturbances in orientation are also associated with substances administered during delivery, such as epidural anesthesia (Sepkoski et al. 1992) and meperidine analgesia (Wittels et al. 1990). The habituation cluster of the

NBAS is similarly related to prenatal exposure to cocaine (Mayes et al. 1993), and the range of state cluster predicts visual processing skills (Moss et al. 1988). Taken together, these observations of maturation, such as vagal tone, state regulation, and neurobehavioural status, can be used as markers of preterm infants' development and the effects of various treatment interventions.

Normally, the period between 32 and 37 weeks' GA is of critical importance for maturation of the vagal tone and circadian systems, owing to cortical maturation, synaptic growth, and rapid myelinization in this period. A reorganization of state regulation occurs in terms of increased quiet sleep and length of the sleep–wake cycle (Curzi-Dascalova et al. 1986). Interestingly, the maturation rate of vagal tone from 33 to 35 weeks GA was found to predict school-age outcomes in preterms (Doussard-Roosevelt et al. 2001). The reports that these maturational indices can be enhanced by environmental factors such as caregiving and nursery conditions (Anders et al. 1985, DiPietro and Porges 1991, Shimada et al. 1999, Mirmiran and Ariagno 2000) suggest that these neurofunctions might be sensitive to intervention. Therefore, it is of major importance to study the specific interventions that might increase the maturation rates of the autonomic and circadian systems during this period in neurodevelopment.

Structured mother–infant skin-to-skin contact (Kangaroo Care, KC), a method first applied to preterm infants in Bogota, Columbia at a time of incubator shortage (Sloan et al. 1994), might promote the maturation of the autonomic and circadian systems. The KC intervention has been reported to improve a variety of functions in preterm infants, including state regulation, heart rate, and respiration (Ludington and Golant 1993, Bohnhorst et al. 2001). These clinical observations in human infants are supported by research in animal models that demonstrated the effects of maternal proximity on newborn animals' autonomic functioning, arousal regulation, and orienting behaviour (Laviola and Terranova 1998, Anand and Scalzo 2000). Different components of the mother's physical presence provided separately to rat pups, such as maternal body heat or smell, regulated specific systems in the pup, such as heart rate and activity level (Hofer 1995). As the KC intervention integrates the rhythmic, thermal, and sensory components of the mother's physical presence, it is proposed that it can affect autonomic functions, state regulation, and orienting behaviour, leading to a more integrated and mature profile.

In view of the above, the present study was designed to examine the effects of KC on vagal tone, state organization, and neurodevelopment in preterm infants. It was proposed that skin-to-skin contact would accelerate the neuromaturation rate and that infants receiving KC would show higher vagal tone and more organized state, in terms of longer periods of quiet sleep and wakefulness and less active sleep states at 37 weeks GA. Additionally, KC infants were expected to score higher on the orientation, habituation, and range of states clusters of the NBAS. Such results would also correlate with our previous observations that KC has a positive effect on the cognitive development of preterm infants (Feldman et al. 2002a).

## Method

### PARTICIPANTS

Seventy low birthweight infants born at the Shaare Zedek Medical Center in Jerusalem with a mean birthweight of 1230g (SD 321.54g, range 540–1650g) and a mean GA of 30.21 weeks (SD 2.16 weeks, range 25–33 weeks) were studied. The study design was case–control; 35 infants underwent KC and 35 matched infants served as controls. Each infant in the study group was matched for sex, birthweight (stratified by 250 increments), GA, medical risk, and family demographics. Infants were excluded from the study if they had intraventricular haemorrhage grades III or IV or suffered from perinatal asphyxia, metabolic disease, or genetic disease or were still being ventilated. All mothers in the study were married to the infant's father, parents had at least high-school education, mothers were at least 20 years old, and all families were considered to have middle and upper-middle socioeconomic status by Israeli standards (Harlap et al. 1977). None of the mothers reported smoking or drug use during pregnancy. Control for demographics included parity (first born versus later born) and maternal and paternal age (ranges: mothers, 21–42 years; fathers, 24–45 years in the two groups) and education (ranges: mothers, 12–20 years; fathers, 12–25 years in the two groups). Family demographics and infant medical information for the two groups are summarized in Table I and show no differences between groups. No group difference was found in mode of delivery, median Apgar scores (8 for Apgar 1 minute, and 9 for Apgar 5 minute in the two groups), nor the amount of breast milk that the infant received.

### RECRUITMENT

Because KC was introduced to the Neonatal Intensive Care Unit (NICU) as a standard clinical option, our Institutional Review Board (IRB) precluded randomization and approved a prospective case–control study. All mothers who met the inclusion and exclusion criteria were offered the option of providing KC. Consecutive mothers who met the study criteria were approached by a nurse who specialized in implementing the KC intervention. Mothers were informed regarding current knowledge of the intervention. To enroll in the intervention group mothers had to agree to perform KC for a least one hour per day for at least 14 consecutive days. On the basis of power calculation (see 'Statistical analyses'), 35 mothers who

**Table I: Family demographic and infant medical variables**

| *Variable* | *KC* | *Control* |
|---|---|---|
| Birthweight, g | 1229.95 (320.21) | 1232.17 (322.15) |
| GA (wk) at birth | 30.28 (2.54) | 30.19 (2.65) |
| Age at entry to study, d | 12.31 (11.03) | 12.70 (11.56) |
| CRIB score | 2.33 (2.98) | 2.35 (2.96) |
| Maternal age, y | 29.17 (4.86) | 29.08 (5.14) |
| Maternal education, y | 14.63 (1.94) | 14.78 (2.14) |
| Paternal age, y | 31.78 (5.86) | 32.14 (7.32) |
| Paternal education, y | 14.17 (2.27) | 14.55 (2.89) |
| M/F ratio | 19/16 | 19/16 |
| Primaparous/multiparous | 15/20 | 15/20 |
| Human milk, % (full, >50%, none) | 25.7, 28.5, 45.7 | 28.5, 20, 51.4 |
| C Section (yes/no) | 25/10 | 24/11 |
| Apgar 1 min | 7.36 (1.97) | 7.52 (1.46) |
| Apgar 5 min | 8.72 (1.23) | 8.63 (1.19) |

CRIB, clinical risk index for babies (International Neonatal Network 1993). Values followed by numbers in parentheses are means (SD).

chose KC and 35 case–control mother–infant dyads were studied. During the recruitment period five mothers refused to participate in the study. Three of these five mothers were approached to participate in the KC group and, although they provided some KC to their infants, they were unwilling to commit to the study's requirements. Two mothers were approached to participate as controls and declined, citing husband's refusal as reasons. There was no difference in the medical or demographic factors between study participants and those who declined to participate. The study was approved by the IRB, and informed consent was obtained from all participants.

### PROCEDURE AND MEASURES

#### *Intervention*

Infants were enrolled at a GA of 31–33 weeks when their medical situation had stabilized. Infants receiving supplementary oxygen by nasal catheter and/or intravenous fluids were included in the study. Infants were enrolled if the mothers agreed to perform KC for at least 14 consecutive days for at least an hour daily. The KC intervention began when the regular nursery routines required that the infants be cared for in incubators, thus precluding direct infant body contact with the caregivers. During this period each infant was fed by gavage tube with either her or his mother's own breast milk or special formula for preterm infants (Similac Premature Formula). Infants who received KC were taken out of the incubator, undressed (wearing only a diaper and sometimes a cap), and placed between the mother's breasts. During KC infants remained attached to a cardiorespiratory monitor and were observed by the nurses who recorded the exact times when the mothers and infants remained in skin-to-skin contact and when the infant returned to standard incubator care. The routine of the NICU was that, after 34 weeks' gestation, infants in both the KC and control groups were fed out of the incubator. There was no difference in the amount of breast milk received by infants in the KC and control groups.

The mean postnatal age of infants' at entry to the KC group was 12.31 days (SD 11.03 days; range 3–40 days) and to the control group was 12.7 days (SD 11.56 days; range 3–39 days),

**Table II: Development of infant state and heart-rate measures from 32 to 37 weeks' gestational age (GA)**

| *Measure* | *32wk GA* | *37wk GA* | *Univariate F* | *p* |
|---|---|---|---|---|
| Infant state organization | | | | |
| Quiet sleep | 0.35 (0.22) | 0.41 (0.18) | 3.86 | 0.041 |
| Active sleep | 0.44 (0.23) | 0.34 (0.19) | 4.95 | 0.023 |
| Sleep–wake transition | 0.09 (0.25) | 0.07 (0.10) | 1.10 | 0.297 |
| Unfocused alertness | 0.06 (0.13) | 0.07 (0.05) | 1.01 | 0.317 |
| Alert wakefulness | 0.02 (0.04) | 0.06 (0.06) | 6.38 | 0.013 |
| Cry | 0.03 (0.05) | 0.04 (0.05) | 0.79 | 0.376 |
| Heart-rate measures | | | | |
| Heart period | 326.21 (21.18) | 317.19 (33.32) | 1.08 | 0.302 |
| Vagal tone (RSA) | 1.30 (1.03) | 1.96 (1.08) | 34.82 | <0.001 |

RSA, respiratory sinus arrhythmia. Numbers for state organization measures represent proportion of time out of 4h observation that infant spent in a designated state. Values followed by numbers in parentheses are means (SD).

**Table III: Infant state, heart-rate, and neurodevelopmental measures in KC and control infants at 37 weeks' gestational age**

| *Measure* | *KC* | *Control* | *Univariate F* | *p* |
|---|---|---|---|---|
| Infant state organization | | | | |
| Quiet sleep | 0.44 (0.19) | 0.38 (0.17) | 5.99 | 0.016 |
| Active sleep | 0.30 (0.15) | 0.39 (0.20) | 8.18 | 0.005 |
| Transition | 0.10 (0.12) | 0.08 (0.10) | 0.40 | 0.528 |
| Unfocused alertness | 0.06 (0.06) | 0.07 (0.06 | 0.11 | 0.737 |
| Alert wakefulness | 0.08 (0.12) | 0.04 (0.07 | 3.78 | 0.050 |
| Cry | 0.03 (0.06) | 0.03 (0.05) | 0.08 | 0.776 |
| Heart-rate measures | | | | |
| Heart period | 319.18 (36.40) | 315.41 (29.72) | 0.34 | 0.562 |
| Vagal tone (RSA) | 2.32 (0.99) | 1.77 (1.10) | 4.98 | 0.029 |
| NBAS | | | | |
| Habituation | 6.71 (0.98) | 6.19 (1.01) | 4.62 | 0.032 |
| Orientation | 5.63 (0.90) | 5.03 (0.87) | 7.15 | 0.007 |
| Range of state | 3.81 (0.54) | 3.77 (0.65) | 1.12 | 0.143 |

Values followed by numbers in parentheses are means (SD). RSA, respiratory sinus arrhythmia; NBAS, Neonatal Behavioral Assessment Scale (Brazelton 1973).

with no group difference. During this period mothers provided on average 29.76 hours of KC (SD 12.86 hours). During KC, mothers were seated in a standardized rocking chair and were provided with a bedside screen to ensure privacy. No change was made to ambient light or sound level in the nursery during KC. During the KC care period infants slept and no feeding was performed. Mothers generally did not talk or sing to the infants during KC. Infants and their mothers were observed and tested before the initiation of KC and before discharge from the hospital (37 weeks' GA). For the control group, the pre-KC observation took place at 32 weeks' gestation, matched to the mean age of the infants when KC was initiated.

*Vagal tone at 32 and 37 weeks' GA*

The infant's heart rate was recorded for about 10 minutes, when the infant was in a quiet sleep state, with the cardiac monitor using a special analog-to-digital adaptor that sampled heart rate, and was transferred into a special computerized system that registered the R waves and computed the R–R interval (i.e. heart period in milliseconds). Vagal tone, the amplitude of respiratory sinus arrhythmia (RSA), was quantified with Porges' MXEdit system (Porges 1985) by a research assistant trained to reliability. After editing of the data to remove artifacts, the MXEdit system converts heart period data into time-based data sampled in 200ms intervals, determines the periodicities of heart rate with a 21-point moving polynomial, filters the time series to extract the heart period within the frequency band of spontaneous breathing of newborn infants, and calculates the vagal tone index. Data from six infants at 32 weeks' GA and from four infants at 37 weeks' GA could not be analyzed because of technical errors. These infants were distributed evenly between groups.

*State observation at 32 and at 37 weeks' GA*

During four consecutive evening hours (19:00 to 23:00) trained coders observed the infants' state in 10-second epochs and entered the data into a computer program. Six states were observed and defined as described by Holditch-Davis (1990), including Quiet Sleep, Active Sleep, Sleep–Wake Transition, Unfocused Alertness, Alert Wakefulness, and Cry.

*Neurodevelopmental status at 37 weeks' GA*

At 37 weeks' GA, infants were examined with the NBAS by a trained neonatologist. Items were composited into six clusters (Lester 1984) and orientation, habituation, and range of state were examined in this study. NBAS test was conducted by a trained neonatologist and the analysis of heart rate and state data was conducted by trained graduate students of psychology who were blinded to group membership of the infants.

*Infant medical risk*

Infant medical risk was quantified by the clinical risk for index for babies (CRIB) score (International Neonatal Network 1993), a measure of risk more accurate than birthweight alone.

*Statistical analyses*

The maturation of heart-rate measures and state organization measures from 32 to 37 weeks' GA was examined with a multivariate analysis of variance (MANOVA) with repeated measures.

MANOVAs with group (KC, control) and infant sex as the between-participant factors were computed for heart-rate measures, state measures, and NBAS measures at 37 weeks' GA to examine group differences.

Hierarchical multiple regressions were computed predicting neurobehavioural status by infant medical risk, vagal tone, state organization, and KC, assessing whether KC contributes to infants' maturation while medical risk and other maturation indices were controlled. The sample provided enough power to detect a large effect size at a power of 0.80 for alpha = 0.05 on all statistical tests (Cohen 1992).

## Results

### MATURATION OF VAGAL TONE AND STATE ORGANIZATION FROM 32 TO 37 WEEKS' GA

Univariate analysis of variance showed no significant difference between groups on heart-rate or state measures at 32 weeks' GA, indicating that the two groups were comparable before the initiation of KC.

*Maturation of heart-rate measures*

Repeated-measures MANOVA computed for the two heart-rate variables (heart period and vagal tone) from 32 to 37 weeks' GA showed maturation across this period; Wilks' $F(2,52)=25.31, p<0.001$. Univariate tests (Table II) showed a significant increase in vagal tone from 32 to 37 weeks' GA, but not in heart period.

*Maturation of state organization measures*

Repeated-measures MANOVA computed for the six states from 32 to 37 weeks' GA similarly showed a significant change with age; Wilks' $F(6,61)=3.37, p=0.008$. During this period quiet sleep increased, active sleep decreased, and periods of alert wakefulness increased (Table II).

Maturation indices that developed with age also show stability of individual differences. Correlation between 32 and 37 weeks' were: $r=0.29$, $p=0.008$ for vagal tone; $r=0.28$, $p=0.009$ for quiet sleep; and $r=0.31$, $p=0.005$, for active sleep. Alert wakefulness was not stable across time ($r=0.08, p=0.44$).

### DIFFERENCES BETWEEN KC AND CONTROLS AT 37 WEEKS' GA

Three MANOVAs with group (KC, control) and infant sex as the between-subject factors examined the differences between KC and controls at 37 weeks' GA. All MANOVAs

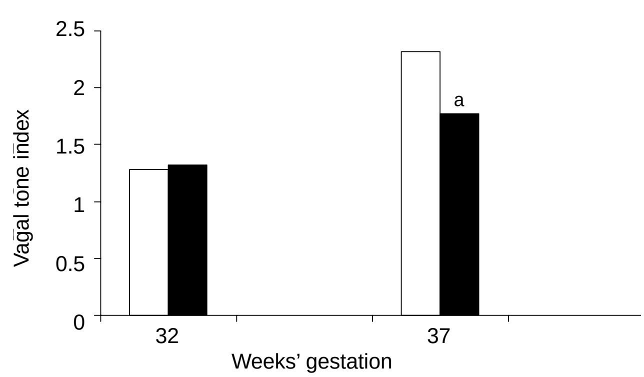


**Figure 1:** *Changes in vagal tone in □ KC and ■ control infants.* [a]*p=0.001.*

showed a significant main effect for group, indicating that at 37 weeks' GA, infants in the KC group showed more mature vagal tone, state organization, and neurobehavioural profiles.

### *Heart-rate measures*

A MANOVA conducted for the heart-rate measures showed a significant overall effect for group: Wilks' $F(2, 58)=4.88$, $p=0.01$. This points to improved autonomic functioning in the KC group. Univariate tests (Table III) demonstrate that KC infants showed significantly higher vagal tone at 37 weeks' GA.

### *State measures*

A MANOVA conducted for the six states at 37 weeks' GA revealed a significant overall effect for group: Wilks' $F$ (5, 58)=3.67, $p=0.006$. This demonstrates a more optimal state organization in the KC group. Univariate tests, reported in Table III, indicate that KC infants spent more time in quiet sleep and alert wakefulness and less time in active sleep.

### *Neurobehavioural measures*

A MANOVA conducted for the three NBAS clusters (habituation, orientation, and range of state) revealed an overall main effect for group: Wilks' $F$ (3, 64)=3.75, $p=0.005$. These findings show that KC infants had more mature neurobehavioural profiles. Univariate tests (Table III) indicated that habituation and orientation improved after KC, whereas no difference was found in the range of states cluster (Figs 1–3).

### PREDICTING INFANTS' NEUROBEHAVIOURAL STATUS

Three hierarchical regressions were computed predicting habituation, orientation, and range of state by neuroregulatory functions. Predictors were entered in four predetermined blocks. In the first block, medical risk was indexed by the CRIB score; in the second, vagal tone at 37 weeks' GA was entered; and in the third, state organization was indexed by quiet sleep, active sleep, and alert wakefulness. In the final step, KC was entered as a binary variable. Results of the three models are presented in Table IV, including the standardized regression coefficients (beta) from the final step, the increment in $R^2$ for each step, the $F$ value for each step, and the $F$ level for the entire model. All variables were normally distributed and outliers were checked before analysis.

The models predicting habituation and orientation were significant, whereas the model predicting range of state was not. Habituation was related to infants' medical condition and to vagal tone. KC had an independent contribution to the prediction of habituation of 8% above and beyond all other variables, and all predictors including KC explained 24% of the variability in habituation. Orientation was independently related to medical risk, vagal tone, and state regulation, namely decreased active sleep and increased alertness. KC had an independent contribution to the prediction of 7% above and beyond all the other variables, and all predictor variables including KC explained 28% of the variability in infants' orientation.

**Table IV: Predicting infants' habituation, orientation, and range of state at 37 weeks' GA**

| *Predictor* | *Habituation* | | | *Orientation* | | | *Range of state* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Beta* | *$R^2$ change* | *F change* | *Beta* | *$R^2$ change* | *F change* | *Beta* | *$R^2$ change* | *F change* |
| Medical risk (CRIB) | –0.18 | 0.04 | 2.30 | $-0.25^a$ | 0.05 | $3.76^a$ | $-0.29^a$ | 0.05 | 2.93 |
| Vagal tone | $0.39^b$ | 0.09 | $6.99^b$ | $0.34^b$ | 0.08 | $6.75^b$ | 0.08 | 0.00 | 0.11 |
| Quiet sleep | 0.12 | | | 0.13 | | | 0.20 | | |
| Active sleep | –0.10 | | | $-0.22^a$ | | –0.08 | | | |
| Alert wakefulness | 0.03 | 0.03 | 1.98 | $0.28^a$ | 0.08 | $4.88^a$ | 0.17 | 0.06 | 1.02 |
| KC | $0.35^a$ | 0.08 | $5.64^a$ | $0.30^a$ | 0.07 | $5.96^b$ | 0.13 | 0.02 | 0.72 |
| $R^2$ total | 0.24; $F(6, 52)=3.77$, $p=0.03$ | | | 0.28; $F(6, 52)=4.53$, $p<0.001$ | | | 0.14; $F(6, 52)=1.53$, $p=0.162$ | | |

$^a p<0.05$. $^b p<0.01$. CRIB, clinical risk index for babies (International Neonatal Network 1993).

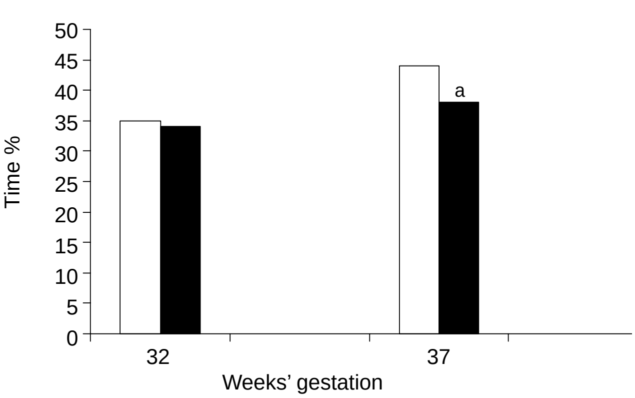


**Figure 2:** *Changes in state organization in □ KC and ■ control infants: quiet sleep.* $^a p=0.016$

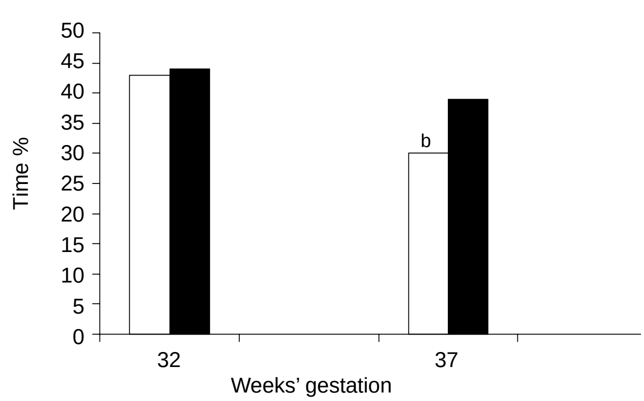


**Figure 3:** *Changes in state organization in □ KC and ■ control infants: active sleep.* $^b p=0.005$

## Discussion

The maturation rate of neurodevelopmental functions in preterm infants is an important index of the adaptive recovery of the CNS from the adverse conditions of untimely birth. Thus, a care intervention that can affect the rate of CNS maturation would have a major clinical importance. Our findings show that mother–infant skin-to-skin contact can affect the rate of autonomic maturation, as shown by greater gains in vagal tone, and can increase the maturation rate of state organization, leading to a more optimal neurobehavioural status at term compared with those infants not receiving KC.

What might be the mechanisms by which skin-to-skin contact affects neurodevelopment? Our findings noted that change after KC was specific to systems that were already in the process of maturation during that period, and to measures that showed stability over time, as demonstrated here and in previous research (DiPietro et al. 1994, Fracasso et al. 1994). This suggests that the KC intervention does not function to awaken immature systems but operates on currently developing systems by altering their growth trajectory to more optimal levels. Thus, the issue of timing in the effects of KC on specific neurofunctions might be of prime importance. The notion of sensitive periods in development as a result of maternal separation has been demonstrated repeatedly in animal research (Laviola and Terranova 1998). Pups separated from their mothers show diminished growth, increased apoptosis, heightened stress reactivity, delayed prefrontal brain growth, and disturbed orientation (Poeggel et al. 1999, Anand and Scalzo 2000, Lehmann et al. 2000), although its applicability to human preterm infants is still not clear. KC was targeted to the period before 34 weeks' GA: a period when full mother–infant body contact is often precluded by nursery routines. After 34 weeks' GA, all mothers began contact with their infants on a daily basis by feeding their infants out of the incubator. However, only the KC group provided direct skin-to-skin-contact for extended periods.

We had previously suggested that the mother's physical contact with her preterm infant through direct skin-to-skin care provides olfactory, auditory, tactile, thermal, and proprioceptive sensory stimulation in a unique interactive style (Feldman et al. 2002b). Previous investigators have noted in both animals and human infants that interventions providing separate components of the 'maternal proximity' constellation, such as maternal odor, massage, or rocking, accelerate physical growth, state organization, and learning (Barnard and Bee 1983, Scafidi et al. 1990, Polan and Hofer 1999, Weizman et al. 1999). Thus, mother–infant physical contact that provides a more global stimulation might not only reverse the negative impact of maternal separation on neurodevelopment but also actually accelerate the rate of maturation compared with infants receiving standardized care.

Interestingly, all measures that improved after KC were related to better infant orientation to the external environment. Such improvement in orientation requires the prior regulation of internal state, which is provided by the mother's physical presence (Hofer 1995). The improvement in vagal tone in the KC group reflects the ability to organize energy and modulate arousal to orient better to subtle environmental changes (Porges 1995). Improvement in state regulation after KC was observed in the increased periods of quiet sleep and alert wake states. It had been shown that the maturity of the circadian system depends on the oscillation between two distinct states: a state (quiet sleep) conducive to rest and a state (wakefulness) that permits effective interaction with the environment. Conversely, immaturity in preterm infants is indexed by higher levels of indeterminate states and is related to poorer cognitive growth (Anders et al. 1985, Beckwith and Parmelee 1986). The habituation and orientation clusters of the NBAS, which index infants' processing skills and orientation to animate and inanimate stimuli, were also improved by KC, confirming that these infants were functioning on a more mature and integrated neurodevelopmental level.

There has been much controversy over the optimal type of developmental intervention that should be provided to the preterm infant. Two seemingly opposing views have been proposed: the first suggests reducing stimulation to a minimum to avoid flooding the fragile infant (Als et al. 1994); the second advocates the need to provide tactile, visual, and auditory stimulation to the understimulated infant (Resnick et al. 1987). These two interventions surprisingly have been reported to result in the same beneficial outcomes (Feldman and Eidelman 1998). We suggest that KC provides a type of controlled and modulated stimulation that integrates the positive features of these two approaches. In addition, KC is consistent with Gottlieb's theory (Gottlieb 1991) on the importance of the sequential development of the senses, namely that in the newborn stage stimulation to the primary senses, touch and proprioception, should be maximized while stimulation to the secondary senses, vision and audition, is minimized. Although there was no difference in the amount of breast milk intake in the KC and control groups, we did not record any data on infant sucking or auto-regulated movement patterns which have been described as neurofunctions that mature with gestational age (Prechtl et al. 1997, Gewolb et al. 2001). Future studies should, therefore, focus particularly on the effect of KC on the development of the suck reflex and the transition to successful breast-feeding in the preterm infant, given its importance for infant nutrition and well-being.

The major limitation of this study relates to the fact that it was not a prospectively randomized study, because randomization was precluded by the IRB (see the Method section). Comparing mother–infant dyads with those previously cared for in our nursery would introduce all the disadvantages and biases of historical controls. In particular, the comparison would be between mothers and infants cared for by different medical and nursing teams and by different treatment protocols. Therefore, we chose a case-control method with careful matching for the variables known to affect neuromaturation, including sex, GA, birthweight, medical condition, amount of breast milk, maternal and paternal age, and educational level of the parents. In addition, infants in the two groups were treated by the same medical and nursing staff with the same medical protocols and in a similar physical environment. Despite this matching, one cannot exclude unknown selection biases, although such biases are unlikely because our end points included objectively measured physiological variables such as vagal tone. The fact that the addition of KC care, particularly in the critical period between 32 and 34 weeks' GA, changed the rate of maturation of the vagal system and the organization of sleep, supports our hypothesis that neurobehavioural development, in both the short and long term, can be effected by changes in the type of neonatal care provided to these high-risk newborn infants (Feldman et al. 2002a). Future studies are needed to delineate the specific factors that mediate these changes in the maturation of infants' nervous systems and to what degree these differences remain as the infants are followed into early childhood and beyond.

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