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Neurophysiologic Assessment of Neonatal Sleep Organization: Preliminary Results of a Randomized, Controlled Trial of Skin Contact With Preterm Infants

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ABSTRACT

BACKGROUND. Sleep is important to brain organization, but few strategies to promote sleep among premature infants have been tested. Behaviorally based measures of sleep have shown increased quiet sleep (QS) and decreased active sleep (AS) during skin-to-skin contact (SSC) with the mother, but these results have not been confirmed with objective electroencephalographic/polysomnographic measures of sleep organization. Important differences exist between behavioral and electroencephalographic/polysomnographic definitions of sleep state.

METHODS. Data for the first 28 relatively healthy, preterm subjects of an ongoing randomized trial of one 2- to 3-hour session of SSC or incubator care between feedings are reported here. Infants were positioned prone, inclined, and nested in an incubator during the 2- to 3-hour pretest period, were fed, and then went into the test period of SSC or incubator care. Infants were left largely undisturbed throughout testing. A mixed-model regression analysis compared the test-pretest differences in outcome measures within and between groups.

RESULTS. Results showed that arousals were significantly lower in the SSC group, compared with the control group, for the entire study period and for test-pretest matched segments of QS and AS. Rapid eye movement was significantly lower for the SSC group for the study period and AS segments. Indeterminate sleep was significantly lower for the SSC group when confounding environmental variables were included in the regression analysis. When 4 subjects who experienced excessive ambient light levels during SSC were removed from analysis, QS increased during SSC.

CONCLUSIONS. The patterns demonstrated by the SSC group are analogous to more-mature sleep organization. SSC may be used as an intervention to improve sleep organization in this population of preterm infants.

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Key Words
electroencephalography, brain maturation, sleep, preterm infants, skin-to-skin contact

Abbreviations
SSC—skin-to-skin contact
PMA—postmenstrual age
IS—indeterminate sleep
AS—active sleep
QS— quiet sleep
EOG— electrooculographic
EEG— electroencephalographic
REM—rapid eye movement
ABSS—Anderson Behavioral State Scale

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ALTHOUGH CONSIDERABLE ATTENTION has been given to preterm infant sleep patterns and the influence of the NICU environment on newborn sleep,[1,2] little attention has been directed to the study of strategies designed to improve sleep organization. One strategy is skin-to-skin contact (SSC). SSC is the upright prone position of the diaper-clad preterm infant skin-to-skin between the mother's breasts. The SSC technique has been shown to alter sleep organization, as measured with behavioral state indices.[3–8] SSC increases the amount of time spent in behaviorally determined quiet sleep (QS)[3,9,10] and decreases the time spent in active sleep (AS)[6,10] and awake states,[6,10] compared with incubator time, regardless of who (mother, father, grandparent, or surrogate parent) provides the SSC.[11,12] The need to verify behavioral sleep findings with more-rigorous neurophysiologic assessments exists because behavioral states among preterm infants are immature,[13] behavioral state assessments are subject to observer bias, and blinding of the observers is not possible. Examining sleep organization with blinded observers scoring from electroencephalographic (EEG)/polysomnographic records would serve this purpose; however, no reported studies that used this method could be found, although neonatal states can be detected with EEG recording as early as 26 to 28 weeks.[14,15]

Important differences in terminology and definitions of neonatal states exist among authors. The definitions used in behavioral observation scales can result in confusion when they are compared with the definitions used for polysomnography. Table 1 compares the definitions in the Anderson Behavioral State Scale (ABSS)[16,17] and the relationship between sleep state and physiologic signals recorded commonly in neonatal polysomnography. It is important to note that AS according to the polysomnographic definition used herein is most similar to the ABSS irregular sleep state and the ABSS active and very active sleep states are most similar to indeterminate sleep (IS) or AS and QS disrupted by microarousals. Finally, the polysomnographic definition of QS is based primarily on the EEG trace discontinu pattern and is associated with, but not defined by, regular respiration, lack of rapid eye movement (REM), and lack of or slight body movements. In contrast, the ABSS regular quiet sleep state is much stricter in excluding any respiratory irregularities and all but slight movement. Furthermore, the ABSS scale uses the highest-numbered state seen within a 30-second epoch, whereas polysomnographic definitions typically use the dominant state within an epoch. On the basis of these differences in definition, reported increases in the ABSS regular quiet sleep state with SSC are analogous to decreases in microarousals during polysomnographic QS. Similarly, reported decreases in ABSS active and very active sleep states are analogous to decreases in microarousals in polysomnographic AS or QS.

SSC provides the infant with physical boundaries (containment), maternal heartbeat sounds, rhythmic movement with maternal breathing, increased body warmth, and prone positioning,[18] ie, simultaneous gentle stimulation across the proprioceptive, auditory, vestibular, thermal, and tactile sensory systems, which contributes to comfort and stabilization of state.[6] Because poor neonatal sleep organization is associated with later developmental disabilities,[19] SSC has been suggested as a simple inexpensive intervention to improve sleep organization.[13]

The purpose of this randomized, controlled trial was to test the effect of SSC on 5 neonatal sleep organization features assessed with EEG/polysomnographic measures at postmenstrual age (PMA) of 32 weeks. The EEG/sleep measures represent different neural networks throughout the neural axis that contribute to sleep organization. Complex interconnections among multiple neuronal networks that subserve sleep allow phenotypic expression of defined states of sleep, arousal, and wakefulness, punctuated by phasic activities such as motor activities (including REM). The effects of SSC on these measures have not been tested previously. We hypothesized that SSC would alter EEG/sleep organization.

METHODS

Design

An institutional review board-approved, pretest-test, randomized, controlled trial was conducted. Seventy-one premature infants were tested between October 2002 and June 2004; data for 28 have been analyzed to date, with 14 in the SSC group and 14 in the control group. Infants were assigned randomly to the SSC or control group with a computerized minimization technique[20] that matched subjects with respect to 5 variables, ie, gender, gestational age, severity of illness (assessed with the Neurobiologic Risk Scale[21,22]), age (in days) at the time of recruitment, and body weight at the time of recruitment. This randomization technique was chosen to maintain equivalence between groups with the inclusion of each new subject.

Subjects

Subjects were recruited before PMA of 32 weeks,[23] after being examined by a neonatologist who determined that the infant had no encephalopathy, intraventricular hemorrhage of more than grade II, white matter lucencies on cranial ultrasound scans, seizures, meningitis, or congenital brain malformations. Subjects whose 5-minute Apgar scores were >6, whose gestational age was ≥28 weeks, and whose testing weight was >1000 g were included. Each infant was fed every 2 or 3 hours through bolus gavage or orally and experienced no painful procedures or sedative medication within 12 hours before testing. Mothers offered no history of prenatal substance abuse.

TABLE 1 **Comparison of ABSS and EEG/Polysomnographic Characteristics of Different Sleep States**

ABSS Terminology	EEG/Polysomnographic Terminology	EEG Findings (Primary Determinant of State)	Eye Movement	Respiration	Heart Rate	Movements
Regular quiet sleep: regular, deep, even respirations; eyes closed; faint or no movement; no REM (slight mouthing or movement of fingers/toes)	QS without microarousals	Trace Discontinu; alternating sleep background/quiescence (2–10 times per minute)	Rare; eyes usually closed (rarely eyes may be slightly open)	Regular (nearly sinusoidal) but may be confounded by waxing and waning of central apneic periods	Steady	Rare and slight, but arousals may disrupt this state briefly
Irregular sleep: irregular respirations; eyes closed; no movement or slight movement of head, face, forearm, hand, fingers, lower leg, foot, or toes (brief apnea)	AS without microarousals (AS is often used interchangeably with REM sleep but we avoid using REM sleep for neonates)	Continuous sleep background activity	REM is a hallmark of AS; occurs in phasic bursting patterns (rarely eyes may be slightly open)	Irregular; characterized by variation in breath-to-breath period and amplitude	More irregular than QS	Frequent small movements of face and extremities; arousals are more frequent than in QS
Active sleep: whole-limb movement (twisting or lifting head or trunk slowly or slightly); eyes closed	AS or QS with microarousals	Brief loss of EEG sleep background activity, often with motion artifacts	Eye movements frequently present; eyes may open	Commonly includes brief disruption of regular breathing pattern		Typically includes movement of extremities and/or EMG activity of face or chin
Very active sleep: total-body movement (twisting or lifting head or trunk; turning head side to side); eyes closed	AS or QS with moderately large arousal	Similar but longer in duration	Similar	Usually chaotic breathing pattern		Larger movement of extremities and trunk and EMG activity of face and chin
	IS	Drowsy or extended arousal or other indefinable state	Similar	Usually chaotic breathing pattern		Usually significant movement and EMG activity
Drowsy: quiet or some movement; eyes dull or glazed; heavy lidded						
Awake states from alert inactivity through hard crying	Awake	No sleep background activity but otherwise varies	Eyes open or opening/closing	Varies		Varies

EMG indicates electromyographic.

Setting

Infants were tested in 1 of the 7 nursery rooms of the NICU or in the step-down unit at Rainbow Infants' and Children's Hospital. Each room accommodates 1 to 6 infants. The step-down unit is composed of private or semiprivate rooms that contain an incubator or crib and sleeping accommodations for the mother. Some rooms have large windows.

Conditions

Recordings were conducted in 2 consecutive interfeeding periods, beginning at approximately 9:00 AM. Infants were left undisturbed between feedings. For the pretest period, all infants wore only a diaper if in an incubator. If the infant was in an open-air crib, then he or she wore a diaper and shirt and was covered with a blanket. In the pretest period, infants were positioned prone at a 30% incline and nested with blanket rolls around the sides and head within a commercially hooded (IsoCover model 92042A-DS; Child Medical Ventures, Boston, MA) OHIO CarePlus incubator (Air-Shields, Philadelphia, PA), or within an open-air crib that was inclined similarly, until the next feeding, which was conducted by a staff nurse. Mothers were absent during the test period if the infant was in the control group. All control group feedings were conducted in the incubator. Control infants continued in the pretest incubator or open-air crib conditions for the test period, whereas SSC infants were positioned with SSC as the mother reclined in a lounger at a 40% incline by the side of the incubator, behind privacy screens. Each mother wore a standard hospital gown and held the infant in a flexed position beneath a receiving blanket folded in fourths. Mothers were asked not to disturb the infant if he or she appeared to be sleeping. Maternal movement was recorded through direct observation and videotape review, to distinguish mother-induced from spontaneous neonatal arousals. Data collection ended when the next scheduled feeding began.

Equipment

A Nihon Koden 9100-PSG EEG system (Nihon Koden, Foothill Ranch, CA) was used to record EEG and polysomnographic data. Data were collected with the Nihon Koden Neurofax software program. Ten-millimeter, gold, EEG electrodes (Grass, Waterford, CT) were placed at standard locations (C3, C4, T3, T4, Cz, O1, O2, and ground). Standard disposable electrodes (Nicolet Biomedical, Madison, WI) were used for polygraphic monitoring of 2 electromyographic electrodes on the chin, 1 electrooculographic (EOG) electrode at the outer canthus of each eye, and 2 electrocardiographic electrodes. Polygraphy also included 2 inductive respiratory bands (Respiband; SensorMedics, Yorba Linda, CA), placed on the chest and abdomen, and 1 pulse oximeter sensor (Masimo SET; Masimo Corp, Irvine, CA), placed over the ball of the infant's foot. Neurophysiologic data were sampled at 1000 samples per second. Ten-20 conductive paste (Weaver, Aurora, CO) was used to affix electrodes to the scalp, with a subset of the standard 10–20 international protocol for electrode placement. EEG, EOG, and electromyographic electrodes with 1.0-m lengths were wrapped together in a stockinette, and the infant's head was covered with a mesh head net (NeuroSupplies, Waterford, CT). Digital EEG data were reviewed and scored with Insight (Persyst, Prescott, AZ), with a sensitivity of 7 μV at 20 seconds per page. Synchronized digital video (model CVXV18NSSEC; Sony, Tokyo, Japan) was also recorded during the study. The study was conducted by a board-certified EEG technician assisted by a skilled neonatal nurse, who annotated the record online for incidental events such as movements, procedures, and environmental occurrences. Ambient light was measured with an EVTECH Instruments lux meter (model L565969; EVTECH Instruments, Taiwan), and sound was measured with a decibelometer (model 33–2055; Tandy Corp, Fort Worth, TX). The light and sound meters were placed near the infant's head in the incubator and on the mother's shoulder during SSC. Light and sound recordings were performed before each study and then every 5 minutes. Infant abdominal skin temperature was recorded with the incubator's thermistor attached 1 cm below the right costal margin on the infant's abdomen, beneath a Mylar patch (Kentex Corp, Irvine, CA). All instruments were autocalibrated.

Recording Procedure

After parental signatures on the institutional review board-approved consent form were obtained, the day for study was scheduled within 2 weeks of the infant having a PMA of 32 weeks. When the 9 AM feeding was over, an event marker was activated, signaling the beginning of data collection. A second event marker signaled the end of the pretest and test periods. SSC mothers arrived 30 minutes before the feeding that concluded the pretest period, so that they could change into the hospital gown and pump breast milk, as needed. SSC mothers were then seated in the recliner and given their infants before the feeding. Infants were fed in the SSC position. When either 120 minutes (for feedings every 2 hours) or 180 minutes (for feedings every 3 hours) of SSC were completed, data collection ceased and the infant was returned to the incubator, after which the electrodes were removed.

Visually Scored EEG Sleep Measures

Measurement

Rudimentary QS, AS, and IS measures were derived through visual scoring of EEG continuity, discontinuity, and arousals.

QS

Electrographically, quiescence or discontinuity (trace discontinu) is the primary measure defining rudimentary QS among preterm infants of <36 weeks' PMA.[24] It is characterized by periods of low-amplitude EEG activity (<20 μV, excluding artifacts) across all channels, typically having a duration of 2 to 10 seconds and repeating 3 to 8 times per minute. A trained neonatal neurologist marked the beginning and end of all discontinuity segments throughout the record.

AS

Continuous EEG sleep background activity characterizes AS. REM is usually present during AS and was used as an outcome measure but was not used to define AS. Periods of continuous EEG activity with no discontinuity for ≥60 seconds and <30 seconds of microarousal were defined as rudimentary AS.

Arousals

Arousals punctuate the underlying EEG continuity-discontinuity architecture. EEG arousal is characterized by a desynchronization or change in the EEG pattern (loss of sleep background activity), which usually is associated with body movements, muscle activity, alterations in the respiratory pattern, and/or eye opening.[25–28] In this analysis, a microarousal (<30 seconds) is a brief disruption of the ongoing state and is not scored as a change in state. In polysomnographic tracings, there is often little distinction, other than duration, between microarousals, more-extended arousals, and IS. This is significantly different from a behavioral state scale that assigns a change in state to a brief microarousal.

IS

Epochs that did not show normal continuous or discontinuous sleep background activity or contained >30 seconds per minute of arousal were defined as IS.[29] In polysomnographic tracings, there is often little distinction, other than duration, between microarousals, extended arousals, and IS. This is significantly different from a behavioral state scale that assigns a state change to even a very brief microarousal.

Cycling Architecture

A macroscopic sleep cycling architecture encompasses the microstructure of preterm neonatal sleep features. Typically, neonatal sleep states cycle between QS (for ~20 minutes) and AS (for ~40 minutes), with varying degrees of arousal and IS scattered throughout both QS and AS. The scoring of EEG sleep measures was performed on a continuous time basis. The raw scoring was aggregated into minute-by-minute epoch state scores with computerized analysis. Commonly, investigators use smoothing or filtering techniques to aggregate states over several minutes.[24,30] In this analysis, the onset of QS was defined as the beginning of a segment in which 3 consecutive minutes or 3 of 4 consecutive minutes were scored as QS. Similarly, the onset of AS was defined as the beginning of a segment in which 3 consecutive minutes or 3 of 4 consecutive minutes were scored as AS. In general, the onset of a state was not allowed at the first epoch of a recording. Cycle duration was defined as the time from the onset of QS through a required period of AS (and IS if present) to the onset of the next QS segment. QS duration was the time from the onset of QS to the onset of AS, excluding any IS epochs at the transition. AS duration was the time from the onset of AS to the onset of QS, excluding any IS epochs at the transition. Typically, 1 or 2 complete sleep cycles were recorded per test or pretest period, with additional partial cycles occurring at the beginning and end of each period. Understanding this macrostructure is important to understanding how and why QS, for example, can contain a finite percentage of AS, percentage of IS, and seconds of arousal.

Outcome Measures

Twenty-one outcome variables were analyzed. The measures were selected to encompass a broad range of physiologic sleep parameters. Some measures were based on visual scoring, and others were based on computerized analysis. Each measure was summarized for both the test and pretest periods. All outcome measures were analyzed as test-pretest changes. Most measures were summarized across study periods (the whole test period, compared with the whole pretest period), but several measures were summarized across comparable test and pretest segments of rudimentary QS or rudimentary AS, where appropriate. The measures were as follows.

Changes in discontinuity were measured across the study period and within QS. The outcome measures were defined as the test-pretest change in the mean percentage of time occupied by discontinuous segments.

Changes in REM counts were measured across the study period and within AS. Rudimentary AS among preterm infants of <36 weeks' PMA is defined by periods of continuous EEG sleep background activity (no discontinuity)[24] and is usually associated with eye movements. Technically, REM is a rapid lateral movement of both eyes that is characterized by a classic signature waveform on a polysomnographic recording. For term or older infants, children, and adults, REM can be scored easily from polysomnographic records; among young preterm infants, however, the electrical signal produced by the immature retinas is very weak. Therefore, in this study we relied on a combination of direct visual and video observation of eye movements and scoring of REMs from the polysomnographic record. The REM count outcome measures were defined as the test-pretest change in the mean percentage of 10-second epochs that con-

tained ≥1 polysomnographic REM or visually observed eye movement.

Changes in arousals were measured across the study period and within QS and AS. EEG arousal is defined as a desynchronization of the EEG activity (loss of sleep background activity), which is usually associated with body movements, muscle activity, alterations in the respiratory pattern, and/or eye opening.[16,28] The arousal outcome measures were defined as the test-pretest change in the percentage of time of microarousal and extended arousal within the respective time periods.

Changes in the mean duration of the cycle, QS, and AS were measured. Rudimentary QS, AS, and IS (as defined above) were derived from visual scoring of EEG discontinuity and arousals. The mean duration outcome measures were defined as the test-pretest change in cycle or segment duration.

Changes in percentages of QS, AS, and IS were measured. States were scored on a continuous basis, not epoch by epoch, although many analyses were summarized on a minute-by-minute basis. The percentage of each state was the total percentage of the study period (test or pretest) that was occupied by that state, with QS being discontinuous EEG activity excluding any microarousals, AS being continuous EEG sleep background activity excluding any microarousals, and IS encompassing any arousals, IS, and rare wakefulness. The outcome measures were defined as the test-pretest change in percentage for each state.

Changes in the respiratory ratio and respiratory rate were measured. The respiratory ratio is a computer-calculated measure of the regularity of respiration. It is a measure of the spread of energy in the frequency domain. A sinusoidal signal has all of its energy focused at a single frequency, resulting in a respiratory ratio of 0. The energy of a chaotic signal is spread very widely across the frequency spectrum, with a respiratory ratio approaching 1. In general, the regular respirations of QS have a low respiratory ratio, the irregular respirations of AS have higher values, and the chaotic respirations of IS have the highest values. The respiratory rate was taken from a measure of the center frequency in the respiratory ratio calculation. These 2 outcome measures were the test-pretest changes calculated from the minute-by-minute averages for each subject.

Changes in the EEG β/α ratio and EEG left/right hemisphere correlation were assessed. These 2 measures were derived from computer calculations of the EEG signals. Historically, neurologists have separated the EEG frequencies into several bands, including α (8–13 Hz) and β (13–22 Hz). The EEG β/α ratio is a unitless measure of the energy in the β-band versus the energy in the α-band, which shows fairly robust changes between QS and AS; it is a modification of measures described by Scher et al.[31–33] The measure was calculated for a number of electrode pairs for each minute, expressed in logarithmic units. The median value across the electrode pairs was used because it limits the effects of artifacts if they are present in a limited number of channels. The EEG left/right hemisphere correlation was calculated as the cross-covariance between the C3-T3 (left) and C4-T4 (right) homologous electrode pairs. The measure was selected because it changes with age and development. The EEG outcome measures were the test-pretest change in the minute-by-minute values averaged over the study period.

Changes in heart rate mean and SD and blood oxygen saturation mean and SD were measured. The oximeter averaging time was set to 2 seconds. The means and SDs of the heart rate and blood oxygen saturation values measured with the Masimo pulse oximeter were calculated for each 1-minute epoch. Each outcome measure was the test-pretest change in the minute-by-minute values averaged over the study period.

EEG/Sleep Record Analysis

A single neonatal neurophysiologist (M.S.S.), who was blinded with respect to both study group and pretest-test periods, visually analyzed all records. Digital annotations were made on each record, marking the beginning and end of each interburst interval (measure of discontinuity), the beginning and end of each arousal, and each REM (identified as an out-of-phase signal on the 2 EOG channels). Each record was reviewed multiple times by the same reader, to determine whether notations had consistent entries (eg, beginning and end of interbursts and arousals and REM occurrences). The raw annotations made by the technician and neurophysiologist were transferred into a database, where they were checked again for consistency and then used in analyses of the sleep architecture.

Statistical Plan

Differences between groups in outcome variables were tested with regression analyses. For each outcome variable, the test period value minus the pretest period value difference was analyzed. For interpretation of results, values statistically near 0 (*P* values not significant) indicate no measurable change in the test period, compared with the pretest period; positive values indicate an increase in the variable during the test period; and negative values indicate a decrease in the variable during the test period. The units of the β coefficients are those of the underlying variables. For example, if a percentage decreases from 12% to 8%, then the β coefficient would be −4%. The primary indicator variable (SSC group) equals 1 for the SSC group and 0 for the control group. The pretest values of all outcome variables were measured under control conditions and thus cannot be related to the SSC intervention. Therefore, the pretest value of each outcome variable was included as a control factor in the regression analysis, to account for baseline

differences between infants. The regression equation for an example outcome variable, X, is $Y_{Xi} = \beta_{o\_X} + \beta_{SSC\_X} \times (\text{SSC group})_i + \beta_{pretest\_X} \times (X_{i\_pretest} - X_{pretest\_mean}) + \epsilon_{Xi}$, where Y_{Xi} is fit to the test minus pretest difference X for the ith subject, β_{o_X} is the average X for the control group, β_{SSC_X} is the change in X (the effect) attributable to SSC, $\beta_{pretest\_X}$ is the adjustment for baseline differences among the infants, and ϵ_{Xi} is the residual error not explained by the regression model. All statistical results are reported as β coefficients (effect size) and their P values, which indicate whether the β coefficients are statistically different from 0. Significance was set at $P \leq .05$.

The effect of potential confounding variables was also analyzed by adding the effects of confounding variables to the regression equation given above, ie, $Y^*_{Xi} = Y_{Xi} + \Sigma_j [\beta_{Cj\_X} \times (C_{ji} - C_{j\_mean})]$, where the effects are summed for each confounding variable, C_j. β_{Cj_X} is the coefficient that describes the reduction in the residual error attributable to inclusion of C_j in the model. With subtraction of the mean value C_{j_mean} from the individual values, β_{Cj_X} causes no net change in the expected value of β_{o_X}. The potential confounding variables included in the analysis were (1) study location (NICU versus step-down unit), (2) length of feeding interval (2 hours versus 3 hours), (3) type of bed unit (incubator versus open-air crib), (4) gender, (5) gestational age, (6) PMA at the time of study, (7) age (in days) on the day of study, (8) birth weight, and (9) study weight.

RESULTS

Demographic Features

Table 2 presents the characteristics of the subjects. No differences between the groups were present, which confirms the balance established by the randomization procedure.

TABLE 2 **Characteristics of the Subjects ($N = 28$)**

Variable	SSC Group ($n = 14$)	Control Group ($n = 14$)
Room, no.		
NICU	7	7
Step-down	7	7
Bed, no.		
Incubator	10	11
Open-air crib	4	3
Feeding schedule, no.		
2-h	7	4
3-h	7	10
Gender, no.		
Female	10	8
Male	4	6
History of apnea/bradycardia, no.		
No	7	7
Yes	7	7
Caffeine on day of study, no.		
No	10	9
Yes	4	5
Gestational age, mean ± SD, wk	30.8 ± 1.4	30.8 ± 1.1
Birth weight, mean ± SD, g	1457 ± 325	1532 ± 241
PMA at time of study, mean ± SD, wk	32.4 ± 0.9	32.5 ± 0.9
Study weight, mean ± SD, g	1487 ± 175	1573 ± 175
Age at time of study, mean ± SD, d	11.6 ± 5.1	12.0 ± 12.0
Neurobiologic Risk Scale score, mean ± SD	0.29 ± 0.47	0.36 ± 0.50
Score of 0, no.	10	9
Score of 1, no.	4	5

Sleep Organization Variables

Regression analysis results for 21 outcome variables without confounding variable effects are reported in Table 3. Significant SSC effects were found in 3 change-in-arousal variables and 2 change-in-REM count variables. With the addition of confounding variable effects, the change in percentage of IS also showed significant SSC effects. The study period was defined as the full test period, compared with the full pretest period. The percentage of time of arousals was significantly lower for the SSC group, compared with the control group, across the study period ($\beta_{SSC} = -7.35$; $P = .015$), as well as during QS ($\beta_{SSC} = -6.61$; $P = .02$) and AS ($\beta_{SSC} = -8.99$; $P = .02$) when analyzed separately. The control group showed a smaller but significant increase in the percentage of time of arousal in the test period, compared with the pretest period ($\beta_o = +4.3$; $P = .037$). The increase in control group arousals was not significant when QS and AS were analyzed separately. Controlling for pretest values reduced significantly the residual regression deviance for most of the outcome variables analyzed (18 of 21 variables; $P \leq .05$). The arousal pretest regression coefficients were $\beta_{pretest} = -0.61$ ($P = .00002$) for QS, $\beta_{pretest} = -0.64$ ($P = .0066$) for AS, and $\beta_{pretest} = -0.51$ ($P = .0075$) for the study period. The sign of the $\beta_{pretest}$ coefficients was negative for all 21 output variables, which indicates that, if a pretest value was higher or lower than the group mean, then the test-pretest difference, ΔX, tended to be in the direction more toward the group mean. In the case of the arousals, if the infant had a particularly high pretest arousal level, then the test period arousal level tended to be a little lower. Conversely, if the pretest arousal level was particularly low, then the test period arousal level tended to be a little higher. Most importantly, with inclusion of the pretest levels in the regression analysis, the baseline scatter was accounted for and the regression analysis was improved significantly.

Two change-in-REM count variables were found to have significantly lower values for the SSC group, compared with the control group. The change-in-REM count values analyzed were the percentage of 10-second epochs that contained ≥1 REM, as recorded either through direct observation during the study or through polysomnographic scoring. REM counts during AS ($\beta_{SSC} = -8.9$; $P = .029$) and during the study period ($\beta_{SSC} = -5.11$; $P = .013$) were significantly lower in the SSC group, com-

TABLE 3 **Regression Analysis Results for Outcome Variables Without Confounding Variable Effects ($N = 28$)**

	β_o	β_{SSC}	$\beta_{pretest}$	P_o	P_{SSC}	$P_{pretest}$
Test-pretest study period						
Change in arousals (% time)	4.3	−7.35	−0.51	.04	.01	.008
Change in REM count	−0.18	−5.11	−0.6	.9	.01	.0006
Change in discontinuity (% time)	−0.006	1.16	−0.59	1	.53	.02
Change in percentage of QS	−1.71	5.35	−0.46	.58	.23	.07
Change in percentage of AS	−1.33	0.49	−0.76	.54	.88	.0002
Change in percentage of IS	2.88	−5.52	−0.59	.2	.1	.003
Change in respiratory ratio	−0.02	−0.02	−0.71	.53	.57	.0002
Change in respiratory rate (breaths per minute)	−4.69	2.04	−0.31	.06	.56	.02
Change in EEG (β/α) ratio	0.004	−0.007	−0.24	.76	.67	.07
Change in EEG left/right hemisphere correlation	−0.02	0.01	−0.64	.17	.57	<.0001
Change in heart rate (beats per minute)	1.43	3.15	−0.29	.25	.08	.04
Change in heart rate, SD	0.6	−0.89	−0.33	.07	.07	.23
Change in oxygen saturation (% concentration)	−0.19	0.000	−0.45	.75	1	.04
Change in oxygen saturation (% concentration), SD	−0.11	0.04	−0.79	.56	.87	<.0001
Test-pretest for matched segments of study						
Change in arousals in QS (% time)	1.22	−6.61	−0.61	.53	.02	.00003
Change in arousals in AS (% time)	4.92	−8.99	−0.64	.06	.02	.007
Change in REM count in AS	−1.48	−8.9	−0.72	.58	.02	.0003
Change in discontinuity in QS (% time)	2.75	−0.37	−0.44	.28	.92	.02
Change in mean QS duration (% time)	0.79	−0.14	−0.48	.63	.95	.002
Change in mean AS duration (% time)	1.38	−6.22	−0.47	.75	.31	.02
Change in mean cycle duration (seconds)	5.42	−10.08	−0.53	.22	.12	.008

pared with the control group. The control group showed no significant difference from 0 (β_o). However, the pretest values contributed significantly to the regression analysis, with coefficients of $\beta_{pretest} = -0.72$ ($P = .0003$) for AS and $\beta_{pretest} = -0.60$ ($P = .0006$) for the study period. Again, the negative sign indicates that outliers in the pretest period tended back toward the mean in the test period.

Regression Analysis With Confounding Variables

As a broad assessment tool, all 21 outcome variables were analyzed by including all confounding variables (except high light exposure) in the regression model, with attention to several important possible concerns, as follows. (1) Were any of the confounders themselves significant? (2) Did they "importantly" change the SSC regression coefficients? (3) Did they change the significance of any regression coefficients? Firstly, with a few exceptions, almost no confounding variables had statistically significant β coefficients. Secondly, the addition of the confounding variables had only minor effects on the SSC coefficients and did not change the impact or interpretation of the results. Thirdly, the confounding variables often improved the fit (reduced the P values) of the SSC coefficients; in other words, they better explained the scatter in the data, although they were not themselves significant, given $N = 28$. Five outcome variables (changes in arousals, percentage of IS, percentage of QS, REM counts, and heart rate means across the study period) were analyzed in more depth after the initial confounding variable analysis. In the analysis, the least-significant confounding variables were removed from the analysis in a stepwise manner, until only the most important confounding variables remained in the regression model. Table 4 reports the regression results for these 5 outcome variables, controlling for confounding variables. The analysis was performed for all variables, but these variables were chosen because the SSC effect was significant when controlling for confounding variables. The change-in-arousal and change-in-REM count variables (described above) during QS and AS are not shown but reflect similar changes.

Table 4 shows the β coefficient, SE, t value, and P value for each input variable included in the model, as well as the degrees of freedom and the overall (null) deviance and residual deviance not explained by the regression model. For each outcome variable, 2 or 3 regression results are shown, ie, (1) without confounding variables, (2) with the 3 most-significant confounding variables, and (when significant) (3) with the same variables plus the variable high light. High light exposure is not a strictly confounding variable because it is not a pretest variable. Rather, it is derived from measurements of light levels during the pretest and test periods. Light levels could be controlled fairly consistently for recording sessions conducted in the private or semiprivate rooms of the step-down unit but not in the NICU. The light could be controlled to some degree in the incubator portion of NICU studies. In 4 of the SSC studies reported here, the light was substantially higher in the test period,

TABLE 4 **Regression Analysis Results for Selected Outcome Variables With Most-Significant Confounding Variable Effects ($N = 28$)**

Test-Pretest Differences Across Study Period	β	SE	*t* Value	*P* Value	Residual Deviance	Degrees of Freedom
Arousals (% time)					2002.9[a]	27
Without confounding variables						
Intercept	3.7	2	1.9	.07	1320.4	25
SSC group	−7.3	2.8	−2.6	.01		
Pretest	−0.5	0.2	−2.9	.008		
With confounding variables but not high light						
Intercept	4.7	1.8	2.6	.02	910.5	22
SSC group	−9.3	2.6	−3.6	.002		
Pretest	−0.5	0.2	−3.2	.004		
2-h versus 3-h feeding	−6.1	3.1	−2	.06		
Incubator versus crib	6.2	3.5	1.8	.09		
PMA	−2.8	1.7	−1.7	.10		
With confounding variables including high light						
Intercept	4.4	1.7	2.6	.02	755.9	21
SSC group	−11.2	2.6	−4.3	.0003		
Pretest	−0.5	0.1	−3.1	.005		
High light	8.4	4.1	2.1	.051		
Incubator versus crib	6.9	3.3	2.1	.048		
PMA	−2.9	1.6	−1.9	.08		
2-h versus 3-h feeding	−3.7	3.1	−1.2	.25		
Percentage of IS					2290.6[a]	27
Without confounding variables						
Intercept	2.9	2.2	1.3	.2	1591.4	25
SSC group	−5.5	3.2	−1.7	.097		
Pretest	−0.59	0.18	−3.2	.003		
With confounding variables but not high light						
Intercept	3.9	2.1	1.9	.08	1219.5	22
SSC group	−7.6	3.1	−2.4	.024		
Pretest	−0.61	0.17	−3.5	.002		
Incubator versus crib	7.6	4	1.9	.07		
PMA	−2.9	1.9	−1.5	.15		
2-h versus 3-h feeding	−5.4	3.6	−1.5	.15		
With confounding variables including high light						
Intercept	3.5	2.1	1.7	.1	1099.4	21
SSC group	−9.0	3.2	−2.8	.01		
Pretest	−0.55	0.17	−3.2	.004		
High light	7.5	5	1.5	.14		
Incubator versus crib	8.3	4	2.1	.049		
PMA	−2.9	1.9	−1.6	.13		
2-h versus 3-h feeding	−3.0	3.8	−0.79	.44		
Percentage of QS with high light-exposed infants removed					3017.7[a]	23
Without confounding variables						
Intercept	−1.6	3.0	−0.5	.61	2665.3	21
SSC group	5.9	4.7	1.2	.23		
Pretest	−0.4	0.3	−1.3	.21		
With confounding variables						
Intercept	−3.7	3.2	−1.2	.26	2058.8	18
SSC group	10.3	5.0	2.1	.05		
Pretest	−0.4	0.3	−1.6	.13		
Study weight	10.9	8.5	1.3	.21		
Incubator versus crib	−14.8	6.8	−2.2	.04		
Gestational age	−9.9	7.1	−1.4	.18		
REM count					1192.1[a]	27
Without confounding variables						
Intercept	2.6	1.4	1.9	.07	638.2	25
SSC group	−5.1	1.9	−2.7	.01		
Pretest	−0.6	0.2	−3.9	.0006		
With confounding variables						
Intercept	2.6	1.3	2	.06	488.4	22
SSC group	−5.1	1.8	−2.8	.01		
Pretest	−0.7	0.2	−4	.0006		
Incubator versus crib	−4.8	2.5	−1.9	.07		
Gender	−3.9	2.1	−1.9	.07		
Gestational age	2.3	1.2	1.8	.08		

TABLE 4 **Continued**

Test-Pretest Differences Across Study Period	β	SE	*t* Value	*P* Value	Residual Deviance	Degrees of Freedom
Heart rate mean					703.3[a]	27
Without confounding variables						
Intercept	−1.6	1.2	−1.3	.21	511.0	25
SSC group	3.2	1.7	1.8	.08		
Pretest	−0.3	0.1	−2.2	.04		
With confounding variables						
Intercept	0.7	1.06	0.66	.51	268.9	20
SSC group	4.6	1.56	2.95	.008		
Pretest	−0.14	0.13	−1.07	.3		
Birth weight	0.039	0.01	3.47	.0026		
Study weight	−0.03	0.01	−2.4	.027		
Age	0.6	0.22	2.67	.015		
Gender	3.56	1.67	2.13	.046		
PMA	−2.09	1.11	−1.89	.075		
NICU	4.2	2.29	1.83	.082		

[a] Null deviance.

compared with the pretest period (more than sevenfold increase in mean lux value) (Table 5). These 4 studies were designated with the high light input variable. The overall (null) deviance is a measure of scatter in an outcome variable without accounting for any regression effects. The residual deviance is a measure of the remaining scatter in the outcome variables after accounting for any regression effects.

For the first outcome variable (change in arousal across the study period), the 3 most-significant confounding variables were 2-hour versus 3-hour feeding interval, incubator versus crib studies, and PMA of the infant. The overall deviance of the change in arousals was 2002.9. The primary regression analysis presented in Table 4 reduced the deviance to 1320.4, which was further reduced to 910.5 with the addition of 3 confounding variables and to 755.9 with the further addition of high light. Although none of the confounding variables or high light exposure showed remarkably strong effects, the variables served to improve the regression analysis, with β_{SSC} showing more strongly lower values and greatly increased significance levels ($P = .002$ and $P = .0003$, compared with $P = .01$ without confounders).

When confounding variables were added to the regression analysis for change in percentage of IS across the study period, the results paralleled those for change in arousals. The overall deviance of change in percentage of IS decreased from 2290.6 to 1591.4 with the primary regression analysis, was further reduced to 1219.5 with the addition of confounding variables, and was reduced to 1099.4 with the further addition of high light. Again, none of the confounding variables or high light showed remarkably strong effects, but the variables served to improve the regression analysis, with β_{SSC} showing more strongly lower values and increased significance levels ($P = .024$ and $P = .01$, compared with $P = .097$ without confounding variables). Change in percentage of QS reached significance only when the 4 neonates with high light exposure were eliminated from the regression analysis.

When confounding variables were added to the regression analysis for change in REM counts across the study period, the regression analysis showed a modest reduction in residual deviance, but the variables had virtually no effect on the primary effects. The variable high light also had no significant effect on the regression analysis and so was not included in Table 4.

When confounding variables were added to the regression analysis for heart rate mean across the study period, the result was quite different from the results for the variables reported above. Four confounding variables were found to have significant effects; in order of significance, they were birth weight, study weight, age (in days), and gender. Two additional variables (PMA of the infant and study location) were included in the regression analysis but were not shown to be statistically significant. With inclusion of these confounding variables, SSC was shown to have a significant effect on mean heart rate ($\beta_{SSC} = 4.8$; $P = .008$). Because the outcome variable was the test-pretest difference, the significance of the confounding variable coefficients indicates that there is an afternoon versus morning relationship between heart rate and the combination of these 6 confounding variables. The confounding variables taken individually did not show any significance.

TABLE 5 **Summary of Light Levels During Studies**

	Light Level, Mean ± SD, lux	
	Pretest Period	Test Period
4 subjects designated by high light = 1	28.6 ± 11.5	207 ± 134
24 remaining subjects with high light = 0	16.3 ± 11.9	15.3 ± 11.1

DISCUSSION

The results show benefits of SSC for neurophysiologic organization of sleep among preterm infants with PMA of 32 weeks; all benefits were independent of any sleep position-related changes in respiratory rate, heart rate, and oxygen saturation. The benefits included reductions in arousals during both QS and AS in the SSC group and throughout the SSC period. Similarly, the percentage of epochs with ≥1 REM decreased significantly during the SSC period and during AS in the SSC group, compared with the control group. These changes were independent of the confounders, including sleep in the home-like step-down unit, rather than in the NICU. The lack of differences attributable to multiple confounders supports the robust effect of SSC without contaminants.

The mean percentage of time of arousals decreased during the SSC period in all measures and increased (albeit insignificantly) during incubator care and in the control group in all measures. These data suggest that the decreases in arousals seen in EEG sleep recordings might be equivalent to the reported increases in behaviorally based QS that have been seen in the multiple behavioral state studies of SSC, especially if linearity is assumed. At 32 weeks' PMA, relatively healthy preterm infants experience fewer and shorter arousals during QS than during AS.[28,32]

A decrease in arousals is a positive change for preterm infants. A pattern of decreased arousal is consistent with more-mature sleep organization and maturation of specific neuronal processes of the central nervous system.[34] A study of breastfeeding mothers found greater central nervous system maturity, as measured by increased QS and decreased arousals, among infants of breastfeeding mothers who had high levels of docosahexaenoic acid, a long-chain polyunsaturated fatty acid that correlates positively with enhanced central nervous system integrity.[35] A decrease in arousals also suggests better sleep organization, with the infant sustaining sleep states for longer time periods. Fewer arousals may have physiologic benefits as well, in part because arousals have been linked to apnea among spontaneously breathing infants.[13]

A possible explanation for decreased arousals from QS and AS during SSC may be intensification of the prone position when the infant is on the mother's chest. Prone position itself decreases arousals. At 36 to 38 weeks' PMA, arousal from AS and QS is less likely to occur when the infant sleeps prone.[36] Because the SSC infants were in the prone position during the pretest period and because the control infants were positioned prone in the incubator throughout the pretest and test periods, maternal influences intensifying the prone position experience during SSC might have had a role. For example, the infant might hear maternal heartbeat sounds during SSC; heartbeat sounds induce sleep.[37] When heartbeat sounds are coupled with gentle rocking (somewhat similar to the rhythmic rise and fall of the mother's chest as she breathes), earlier development of distinct sleep patterns occurs[38] and the amount of QS increases.[39,40] SSC includes an element of containment, in that the infant is placed prone between the mother's breasts, beneath a blanket, with the mother's arms holding the infant in place. Containment evokes quiescence and the onset of QS,[41] as well as a decrease in arousals from QS.[42] Therefore, the SSC prone position plus containment may be more potent than the prone position alone in changing arousals. Another possible explanation for the decrease in arousals during SSC may be that SSC in some way increases the arousal threshold in QS and AS, although increases in arousal threshold during QS among preterm infants are not usually seen until 44 to 45 weeks' PMA.[43]

The reductions in arousals and REM counts were clearly the most robust findings of this investigation and were independent of environmental conditions. However, other indicators of sleep organization may be responsive to environmental influences. To look at this possibility, we examined the influence of other confounders. We found that the presence of high light levels in the NICU outside the incubators influenced several sleep indices. When the light level was much higher during the SSC test period, compared with the pretest period, the amount of QS did not increase and instead decreased slightly. The decrease failed to reach statistical significance ($n = 4$) but showed an influence of ambient lighting on QS. A mixed-model regression analysis was performed after removal of the 4 subjects who were tested under the high lighting condition ($n = 24$). Significant changes from the pretest period to the study period in the SSC group were seen in percentage of QS (increase; $\beta = +10.3$; $P = .05$), percentage of IS (decrease; $\beta = -9.9$; $P = .008$), arousals (decrease; $\beta = -10.3$; $P < .0005$), and REM counts (decrease; $\beta = -5.1$; $P = .02$). Percentage of QS increased significantly when ambient light was <240 lux. These findings are in contrast to those of Hellstrom-Westas et al,[44] who found no differences in duration of and percentage of time spent in QS, with amplitude-integrated EEG recording, when 32- to 34-week preterm infants were in a hooded incubator that provided low ambient light levels or in an uncovered incubator that provided high illumination levels. The conflict may be explained by the difference in being in an uncovered incubator, for which light levels are still lower than outside the incubator, although overhead lighting is similar.[45] Also the studies by Hellstrom-Westas et al[44] were single-channel recordings, which might not have detected state-specific changes as accurately as complete EEG/sleep recordings. Low lighting levels in the NICU may be a conservative approach until more is known concerning the impact of illumination on the early development of visual systems and sleep organization. Reduced-lighting studies have shown no negative effects on preterm infant vision[46] and no differ-

ences in medical outcomes.[47] Future studies that evaluate polysomnographic sleep under low and high lighting conditions are needed.

The increase in QS in the SSC group is an encouraging finding, because QS is needed for brain maturation. Hippocampal processing of waking experiences occurs during QS,[48] and preterm infants need a dominance of QS before being able to express AS.[49] The succession of REM sleep after QS also plays an important role in memory processing, because certain types of memory are laid down in QS[50,51] and other types of memory are processed in AS.[52,53] As the premature infant matures, the percentage of time in QS increases. Increased duration of QS requires the greatest amount of neural control, making QS the most organized sleep state.[54]

No changes in respiratory rate and oxygen saturation between the periods or for the SSC group were seen. These data confirm cardiorespiratory stability during the pretest and test periods for both groups and are similar to previous findings with SSC.[7,55–57] Heart rate did increase during SSC when the influence of confounding variables was controlled. Heart rate increased by ~10 beats per minute during SSC, similar to previous SSC findings[7,58] and within the range expected because of increased body temperature,[7,59] upright position of SSC[57,58] or upright position alone,[60,61] or being in the prone position during QS episodes.[62]

Our findings showed no difference in changes in sleep parameters when infants were observed in the NICU or in a home-like step-down unit. This is not surprising, because the pretest-test design of the study was intended to control for these factors. However, additional analysis is warranted to assess whether any of these confounding variables were correlated with baseline sleep parameters (not changes in parameters). It was suggested that we may wish to analyze the effects of other confounding variables, such as history of apnea of prematurity and caffeine administration, as well as analyzing the effect of SSC on apnea and bradycardia and their correlations with the well-documented temperature effects of SSC.

Firstly, a contribution of this study is that it is the first report of a neurophysiologic method for accurate state assessment while an infant is being held by his or her mother. Secondly, the randomized, controlled design removed the effects of multiple confounders that cannot be controlled for when clinical trials are conducted with preterm infants. Thirdly, the minimization technique is a useful method of randomization when numerous confounders are anticipated.

Because promotion of sleep organization is so important for normal neurodevelopment, one would expect that the infant's sleep status could guide clinical care. However, this is not yet a well-defined goal for physician or nursing personnel. In general, developmental care instructs that care should be based on the infant's individual ability to handle the stimulation provided by the caregiver, by the physical environment, and by parental contact, without promoting autonomic and behavioral disorganization. The goal of developmental care is to promote stable, well-organized infants who can conserve energy for growth and development.[63,64] Physiologic stability can be promoted through the use of SSC, as reflected by behavioral state stability.[13] Although state organization is also a laudable goal for developmental care,[65] state organization is not a primary focus of developmental care among NICU staff members. Nurses do not assess systematically the levels of sleep or wakefulness among infants,[66] although responses to interventions are mediated by state transitions. Caregiving itself influences state expression; QS increases if infants are undisturbed, whereas waking states increase when caregivers interact with children.[1,67] In fact, 50% of premature infants in one study did not experience any waking before nursing interventions,[68] and subsequent nursing interventions disrupted sleep predominantly. The more intrusive the care, the more disruption to sleep there is, as measured with transitions from sleep to wakefulness. Nurses have been taught that developmental care means reduction of stimulation to the infant, especially tactile stimulation.[69,70] Minimal handling, including minimal handling and holding by parents, is considered desirable.[69] As minimal handling protocols have become common, noxious handling has not been differentiated from beneficial handling. Gentle human touch has multiple benefits for preterm infants, which are seldom acknowledged.[71] Parental involvement is an inherent component of SSC, and clearly SSC is a form of beneficial handling, assuming that stimulation is mediated through the limbic system.[72] Parental involvement in NICU care is recommended but has advanced slowly.[73,74] SSC is not practiced routinely in the United States,[75] although its implementation is increasing[76] and it is recommended as a strategy to increase parental involvement and to provide infants with pleasing experiences.[77,78] Because the beneficial effects of improved sleep organization on neurodevelopment are gradual and subtle, SSC should be practiced more widely for extended periods during postnatal life.

Previous research showed that the physiologic and behavioral state effects of SSC are not sustained once SSC is discontinued,[9,58,59,79–83] which suggests a limited impact from just 1 session of SSC. Repeated use of SSC to improve sleep organization may result in improved sleep organization by 40 weeks' PMA, as a reflection of enhanced neuroplasticity leading to improved neurobehavioral development. Better sleep organization at 40 weeks' PMA might result in sleep among preterm infants that is more similar to that of term infants.[31] Therefore, future studies should measure sleep organization and developmental outcomes after multiple SSC sessions.

CONCLUSIONS

Previous reports advocated environmental adjustments that promote better sleep organization while neonates are in the NICU.[13] SSC can improve the integrity of sleep.[13] Changes in sleep organization reported in this study, namely, decreased arousals, REM counts, and IS, with increased QS percentages, are alterations in sleep organization that may promote improved brain maturation. These data suggest that SSC is a nonpharmacologic interventional treatment that affects sleep organization, and ultimately neurodevelopment, positively.

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