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Neurophysiologic Assessment of Brain Maturation after an Eight-Week Trial of Skin-to-Skin Contact on Preterm Infants

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Abstract

Objective: Skin-to-skin contact (SSC) promotes physiological stability and interaction between parents and infants. Analyses of EEG-sleep studies can compare functional brain maturation between SSC and non-SSC cohorts.

Methods: Sixteen EEG-sleep studies were performed on eight preterm infants who received eight weeks of SSC, and compared with two non-SSC cohorts at term (N=126), a preterm group corrected to term age and a full term group. Seven linear and two complexity measures were compared (Mann-Whitney U test comparisons $p<.05$).

Results: Fewer REMs, more quiet sleep, increased respiratory regularity, longer cycles, and less spectral beta were noted for SSC preterm infants compared with both control cohorts. Fewer REMs, greater arousals and more quiet sleep were noted for SSC infants compared with the non-SSC preterms at term. Three right hemispheric regions had greater complexity in the SSC group. Discriminant analysis showed that the SSC cohort was closer to the non-SSC full-term cohort.

Conclusion: Skin to skin contact accelerates brain maturation in healthy preterm infants compared with two groups without SSC.

Significance: Combined use of linear and complexity analysis strategies offer complementary information regarding altered neuronal functions after developmental care interventions. Such analyses may be helpful to assess other neuroprotection strategies.

Keywords

neonate; developmental care; skin-to-skin contact; kangaroo care; EEG-sleep; brain plasticity

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INTRODUCTION

Neonatal electroencephalographic-polysomnographic studies have been performed for over half a century (Scher 2006). From the earliest days of the development of the neonatal intensive care unit, EEG-sleep studies have been proposed to assess brain organization and maturation, determine the severity and persistence of a neonatal encephalopathy, detect neonatal seizures, and identify associations with serial clinical examinations and neuroimaging studies. Serial EEG-sleep assessments can include both visual and computer analyses to assess brain organization and maturation (Scher 2004).

Since the establishment of the modern neonatal intensive care unit, there has been a growing incidence of premature infants. A recently published report estimates that 12.3 percent of all live births in the United States are children less than 37 weeks gestation (Behrman and Butler 2006). Altered brain structure and function due to conditions of prematurity have been presented. Such changes may influence long-term outcomes (Isaacs et al. 2003) (Scher et al. 2003) (Skranes et al. 2007) (Srinivasan et al. 2007) (Thompson et al. 2007).

Emphasis is now focused on optimizing environmental factors in the neonatal intensive care unit as a form of neuroprotection, particularly light, sound, tactile stimulation and sleep during the long convalescence, in an attempt to shorten hospitalization and improve short-term outcome (Blackburn 1998) (Aucott 2002) (Gary and Philbin 2004). During this extended convalescent time period, environmental alterations include adjustments of light, sound, tactile stimulation and sleep length and quality. The most immature neonates will spend as long as three to four months in the neonatal intensive care unit and are subjected to environmental effects for a longer period of time. Developmentally sensitive carepaths for nurses and physicians have been developed to improve ongoing care for neonates as assessed by sleep, growth and age at discharge (Bertelle et al 2005) (Bertelle et al. 2007).

One developmental care path is skin-to-skin contact (SSC) or kangaroo care (Ludington-Hoe et al. 1994) (Tessier et al. 2003). Past studies demonstrated that this specific developmental care program promotes physiologic stability and parental-infant interactions to facilitate health and improve short and long-term outcomes (Feldman et al. 2002) (Feldman and Eidelman 2003) (Bergman et al 2004). Developmental care practices for the newborn are supported by experimental evidence that maternal care epigentically programs stress responses in offspring with later effects on adult behavior (Szyf et al 2007).

Electroencephalographic/polysomnographic (EEG-Sleep) studies are one method by which one can judge the effectiveness of a neuroprotective protocol such as SSC on neonatal brain organization and maturation. Behavioral and neurophysiological parameters must be rigorously defined to accurately assess neonatal sleep state and transitions between active and quiet sleep segments within the sleep cycle. These parameters can then form the basis for comparing neonates with and without therapeutic interventions. For the comparison of SSC and non-SSC cohorts, we have chosen a neurophysiologic approach using serial EEG-polygraphic data files that were submitted for computational analyses.

The purpose of this study was to extend our initial observations (Ludington-Hoe et al 2006) that a single SSC session at 32 weeks postmenstrual age (PMA) significantly altered EEG-sleep organization in infants assessed. This present study provides evidence that SSC alters neurophysiologic maturation when EEG-sleep studies for a SSC cohort were compared with two non-SSC cohorts using linear and complexity analysis techniques at term ages.

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METHODS

Design

An institutional review board approved a pretest-test, randomized control trial of SSC. Seventy-five preterm infants were evaluated once between October 2002 and June 2004. Longitudinal data for eight infants were collected at both 32 weeks and 40 weeks PMA. Infants in this pilot study were assigned SSC while maintaining the pretest-test randomized assessment for later sleep scoring and analyses as previously described (Ludington-Hoe et al 2006).

Subjects

Subjects were recruited before PMA of 32 weeks, following an examination by a neonatologist who determined that the infant had no encephalopathy, intraventricular hemorrhage of more than grade II severity, white matter lucencies on cranial ultrasound scans, seizures, meningitis, or congenital brain malformations. Infants also exhibited 5-minute Apgar scores >6, were born at a gestational age ≥28 weeks, with a testing weight of >1000 gms at the time of the study. Each infant was fed every 2 or 3 hours by bolus gavage or oral feedings and experienced no painful procedures or sedative medication within 12 hours of the testing protocol. Mothers had no history of prenatal substance use.

Two control cohorts were also recorded at term age. One cohort included healthy preterm infants studied when they reached a corrected term. The second control cohort consisted of healthy full-term infants who were studied 1 to 3 days after delivery. Both control cohorts were recruited for earlier studies at the University of Pittsburgh (Scher et al 2003). EEG-sleep analyses of all infants were recorded on a relational database together with demographic and clinical information. Both the raw EEG-sleep recordings and the visual and digital calculations of physiologic measures were entered into the database.

Research Setting

Infants in the SSC cohort were tested in one of the seven nursery rooms of the NICU or in the step-down unit at Rainbow Babies and Children's Hospital. Each room accommodates one to six infants. The step-down unit consists of private or semiprivate rooms that contain an incubator or crib and sleeping accommodations for the mother. Some rooms have large windows. Studies for the two control cohorts were similarly recorded in either a NICU setting or an EEG laboratory location at Magee-Women's Hospital of the University of Pittsburgh.

Recording Conditions

Recordings were conducted during two consecutive inter-feeding periods, beginning at approximately 9:00 am. Each child received one and one-half hours of SSC, four days a week, for eight weeks. Recording conditions, equipment, and procedures were identical to descriptions provided in earlier publications (Ludington-Hoe et al. 2006, Scher et al 2003). All infants received a diaper change after a feeding, followed by a multiple hour inter-feeding EEG-sleep study. Studies were terminated when the next feeding was required. Infants receiving SSC were studied with an EEG-sleep study for at least one complete sleep cycle before and during skin-to-skin care.

Visually Scored EEG-sleep Measures

Measurement—Rudimentary quiet (non-REM) sleep (QS), active (REM) sleep (AS), and indeterminate sleep (IS) were identified through visual scoring of EEG continuity, discontinuity, and arousals previously defined (Scher et al. 2003). QS, AS and IS measures

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for term infants were similarly identified based on conventional pattern descriptions (Scher 2006). Descriptions for QS, AS, IS, arousals and cycling architecture were identical to an earlier publication (Ludington-Hoe et al. 2006).

Active sleep segments for preterm infants consist of continuous EEG tracings with simultaneously recorded polygraphic parameters documenting rapid eye movements (REMs), body movements and irregular cardiorespiratory rhythms. Conversely, quiet sleep segments for the preterm infants consist of discontinuous periods of EEG consisting of bursts of EEG activity alternating with episodes of continuous EEG activity. Polygraphic parameters are simultaneously recorded to complete the sleep state identification and are comprised of minimal body movements, no REMs and regular cardiorespiratory rhythms.

Active sleep segments for infants at term consisted of two types of continuous EEG background rhythms consist of either moderate or low amplitude activities. Simultaneously recorded polygraphic measures recorded abundant body movements, REMs and irregular cardiorespiratory rhythms. Quiet sleep segments for infants at term consist of two types of EEG background rhythms, either a high voltage slow or a discontinuous type called tracé alternant. Tracé alternant consist of alternating EEG epochs of EEG bursts and quiescent intervals. Polygraphic measured during quiet sleep consist of minimal body movements, no REMs and regular cardiorespiratory rhythms. More completed descriptions of sleep architecture are presented elsewhere (Scher 2006).

Outcome Measures

Twenty-one outcome variables were analyzed, as in the previous study (Ludington-Hoe et al. 2006). Seven measures comprised the physiologic dysmaturity index which collectively has been used to distinguish preterm from full-term sleep organization at term ages (Scher 2004). These measures were previously selected based on statistical assessments to winnow down from thirty-four measures that best represent differences in physiologic neonatal sleep parameters between the cohorts. Some measures were derived from visual scoring, and others were calculated from computerized analyses. 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. Changes in REMs 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), and is usually associated with eye movements. For term infants, AS and QS were defined by electrographic-polygraphic segments, described above that conform to definitions for children >37 weeks PMA.

REMs are rapid lateral movements of both eyes that are characterized by classic signature waveforms on a polysomnographic recording. For term or older infants, children, and adults, REMs 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 observations of eye movements to score REMs from the polysomnographic record. The REMs count measures were recorded for the test-pretest changes in the SSC cohort as the mean percentage of 10-second intervals that contained >1 polysomnographic or visually observed rapid eye movement.

Arousals were measured across the study period for each subject within QS and AS epochs. An EEG or cortical arousal was identified and defined as a desynchronization of the EEG activity (i.e. an abrupt diminution in amplitude), which was usually associated with body

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movements, muscle activity, alterations in the respiratory pattern, and/or eye opening. The arousal numbers and durations were defined for the SSC cohort as the test-pretest changes in the percentage of durations and numbers of arousals within each time period.

The mean duration of the sleep cycle segments QS, IS and AS were measured. Rudimentary QS, AS and IS for the preterm and QS, AS and IS for the term infants (as defined above) were derived from visual scoring of EEG discontinuity and arousals. The duration of the sleep cycles was measured from quiet sleep to quiet sleep segments of at least three minutes duration. Changes in percentages of QS, AS and IS were measured. States were scored on a continuous basis as the duration of particular sleep state. The percentage of each state was the total percentage of the study period (test or pretest) for the SSC cohort that was occupied by that 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 two outcome measures were the test-pretest changes calculated from the minute-by-minute averages for each subject.

Changes in the EEG spectral beta/alpha ratio and EEG left/right hemisphere correlation were assessed. These 2 measures were derived from computer calculations of the frequency content of the EEG signals in both the alpha and beta ranges. The EEG was analyzed as an average across all EEG channels in minute to minute epochs and sampled at a rate of 1 kHz. EEG frequencies are conventionally separated into alpha (8 to 13 Hz) and beta (>13.0 to 22 Hz). The EEG beta/alpha ratio is a unitless measure of the energy in the beta band versus the energy in the alpha band, which shows fairly robust changes between QS and AS; it is a modification of measures previously described (Scher et al. 2003) (Scher et al. 1997). 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 spectral content in left central-left temporal (C3-T3) and right central-right temporal (C4-T4) homologous electrode pairs. The EEG signals in these two channels were analyzed in one minute epochs at a sampling rate of 1 kHz. This measure changes with age and development. This EEG measure compared test-pretest changes for the minute-by-minute values averaged over the study period.

Changes in mean and standard deviation (SD) of heart rate and blood oxygen saturation 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 (Radical model, Irvine California) were calculated for each 1-minute interval. Each measure compared the test-pretest changes for the minute-by-minute values averaged over the study period.

It is well understood that physiological signals, in both health and disease, contain both linear and non-linear sources of variability, in either the frequency or time domain. Linear time domain methods (e.g. mean, variance and coefficient of variation) along with linear frequency domain methods (e.g. frequency band powers) are commonly used to analyze

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EEG signals to distinguish state (e.g. awake and sleep) as well as to distinguish health from disease. To complement our linear analyses of the polysomnographic data, we chose to investigate the application of two complexity measures approximate entropy and sample entropy (Pincus 1991; Richman and Moorman 2000). These measures were used to compare EEG complexity of the SSC cohort to the non-SSC cohort on a channel-by-channel basis. Approximate entropy and sample entropy quantify the complexity of signal in terms of the predictability of patterns in the time series data being analyzed. Entropies are measures of order or organization of the signal either in the frequency or time domain. The essential hypothesis proposes that a signal is less complex if given the existence of a pattern of length m in the data. There is increased prevalence of patterns of length m+1. Hence, approximate and sample entropy quantify complexity in terms of the predictability of patterns in the time series data, with the assumption that an increase in complexity (decrease in predictability). Our hypothesis was that higher complexity would be expressed in the cohort who received SSC compared with two non-SSC cohorts, with the further speculation that higher complexity suggested more advanced brain maturation. Further, discriminant analysis using the Mahalanobis Distance metric was used to make individual, rather than group, assessments between the neonates in the SSC cohort and the two non-SSC cohorts.

EEG/Sleep Record Analyses

A single neonatal neurophysiologist (M.S.S), who was blinded with respect to 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 two electrooculographic channels). Each record was reviewed multiple times by the same reader, to determine whether notations had consistent entries (e.g., beginning and end of interbursts, 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 Analyses

Differences in the outcome variables between the SSC cohort and both non-SSC control cohorts were tested using Mann-Whitney non-parametric U test comparisons ($p < .05$).

RESULTS

Demographic Features

Table 1 presents the eight subjects in the SSC group compared to the 126 non-SSC control subjects with respect to gender, gestational age, birthweight, and postmenstrual age at the study time.

Sleep Organization Variables

Linear Measures—The means and standard deviations for the seven linear measures are listed in Table 2a. Five linear measures distinguish the SSC pilot group from the two non-SSC cohorts and consist of fewer REMs ($p < .0001$), longer sleep cycle lengths ($p = .01$), higher percentage of quiet sleep ($p = .0001$), less spectral beta power ($p = .025$), and increased spectral respiratory irregularity ($p = .02$).

Three linear measures distinguished the SSC pilot group from the non-SSC preterm at term group and included fewer REMs ($p < .0001$), higher percentage of quiet sleep ($p = .0003$), and greater arousals during quiet sleep ($p = .0003$).

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The mean and standard deviation values for the non-linear measures are listed in Table 2b. Five brain regions in the SSC cohort had greater complexity when compared with the non-SSC preterm cohort at the corrected term age. These included specific brain regions in the right hemisphere, as well as, in left and right parasagittal regions corresponding to the electrodes C_4-T_4, T_4-O_2, C_4-C_Z, C_3-C_Z, T_3-C_3.

There were also three brain regions that showed greater EEG complexity for the SSC cohort group when compared with both the preterm and full-term groups from the non-SSC cohort. The regions involved were exclusively in the right hemisphere represented by the channels C_4-C_Z, C_4-T_4, T_4-O_2.

Less complexity was noted in the channels corresponding with the posterior quadrant of the left hemisphere in the SSC cohort, consisting of T_3-O_1, C_3-C_Z, and T3-T3 channels, compared with both non-SSC full term cohorts.

Values for discriminant analyses are listed for each SSC subject in Table 3. Discriminant analysis using the means of the Mahalanobis metric was then used to statistically evaluate the relationship between the complexity measures for each SSC subject compared with both non-SSC cohorts. It was determined that the SSC cohort subject by subject is statistically more similar to the full-term non-SSC cohort than to the non-SSC preterm group.

DISCUSSION

We report more accelerated neurophysiological development for neonates who received skin-to-skin contact (SSC) over an eight-week period using both linear and complexity analyses of EEG-sleep behaviors, compared with two non-SSC cohorts. These behaviors are physiologic surrogates for multiple interconnecting neuronal pathways throughout the neuroaxis within brainstem, diencephalon and cortex which subserve state regulation (Steriade 2006) (Datta and MacLean 2007) (McCarley 2007). Five specific neuronal pathways include the ponto-medullary to basal-frontal pathway subserving respiratory activity, the pedunculo-pontine/geniculocalacarine pathways identified with REM behavior, the ascending reticular activating pathway subserving arousals, the corticothalamic pathways subserving quiet sleep (NREM) expression and the cortico-cortical pathways representing spectral beta power and complexity. Our study results suggest that the immature brain responds differently to the developmental intervention of skin-to-skin contact when compared with groups not receiving this form of developmental care. The present findings reinforce our previous report of more organized sleep behavior after a single SSC session at 32 weeks PMA (Ludington-Hoe et al. 2006) and support previously published findings that a different form of developmental intervention, Neonatal Individualized Developmental Care and Assessment Program (NIDCAP), which also documented accelerated brain maturation (Als et al. 2004), based on EEG and neuroimaging measures. The beneficial results of neonatal developmental practices are also supported by the experimental evidence that maternal care epigenetically programs stress responses in offspring with effects on adult behavior. (Szyf et al 2007).

We previously reported both advanced and delayed expressions of brain function in a healthy preterm cohort at term compared to a full-term cohort, based on a seven-item physiologic dysmaturity index comprised of seven EEG-sleep behaviors (Scher 1997a) (Scher 1997b). This dysmaturity index was derived after winnowing down from thirty-four to seven physiologic measures of EEG-sleep that best differentiated between two cohorts. We also reported that increased complexity was positively associated with brain maturation (Scher 2005) (Janjarasjitt 2008). Combined linear and complexity measures can better reflect the brain's physiologic adaptive response to the conditions of prematurity. This

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biological adaptive process was previously defined as ontogenetic adaptation (Oppenheim 1981), and is now integrated into the contemporary concept of developmental neural plasticity (Cicchetti and Blender 2006). The dysmaturity index, as defined by our research group, represents a physiologic marker of the brain's adaptation to the environmental influences of extrauterine life for a healthy preterm cohort who did not suffer postnatal illnesses (Scher1997a) (Scher1997b). Our findings of altered sleep organization and maturation after the developmental intervention of SSC, further extends this concept of adaptation of a preterm cohort to the therapeutic intervention of one type of developmental care. Given the long convalescent hospitalization of most preterm infants, attention to the maintenance of state homeostasis using various forms of developmental intervention has been emphasized (Bertelle et al. 2007) as a strategy of neuroprotection. SSC appears to accelerate EEG-sleep state organization and maturation as a non-pharmacologic neuroprotective intervention when compared with two non-SSC cohorts. The prolonged benefits of these non-pharmacologic neuroprotective techniques will need to be more systematically studied in different categories of at-risk infants after discharge to the home setting. Recent functional MRI studies of mother's responses to their infant's facial cues emphasize the positive plasticity changes that are documented in the caregiver as a result of an enriched interaction with their infant (Strathern et al 2008). Recommended neuroprotective strategies that are beneficial in group studies, within the Neonatal Intensive Care Unit and at home, need to be tailored for the individual child relative to his/her specific strengths and vulnerabilities.

Our finding of more accelerated (i.e. more complex) right hemispheric maturation for the SSC cohort compared to both non-SSC controlled cohorts is supported by past studies which demonstrated right hemispheric dominance of the immature brain (Chiron et al. 1997, Schore 2001). We speculate that more advanced cortico-cortical connections exist in early life preferentially in the right rather than the left hemisphere, because of the greater responsiveness of the right hemisphere to sensory stimulation. This right hemispheric response to sensory input has been previously demonstrated based on the neonate's response to painful stimuli (Fernandez et al. 2003). Despite a general paucity in the immature brain of cortical lateralization for many functions, the right hemisphere in the neonate demonstrates that more dominant cortical functions are already expressed for spatial sensory representation and arousal in response to positive or noxious stimuli.

To our knowledge, our study is the first to report the impact of SSC on neonatal neurophysiologic maturation over multiple-weeks, using both linear and complexity analyses. Comparisons among SSC studies remain difficult because different methods to access sleep organization were used, different methods of developmental intervention were applied, and environmental variables such as light, sound, and tactile stimulation were not uniformly reported. For example, studies reported no differences in sleep organization with changes in sleep input (Becker et al 1993, Ariagno el al 1997, Hellstrom-Westas etal 2001, Brandon et al 2001, Westrup et al 2002, Mirmiran et al 2003).

Our combined use of linear and complexity analysis methods emphasizes the potential advantage of combining multiple analytic strategies to assess in brain maturation involving multiple interconnected neuronal pathways after neuroprotective interventions. While frequency analyses can best characterize the strength of a regional source by power spectra, complexity analysis methods can interpret physiological behaviors as a measure of the state of a dynamical system. Our research group previously demonstrated how another complexity measure, correlation dimension (CD), can characterize functional brain maturation in preterm populations (Scher et al. 2005) (Janjarasjitt et al. 2008). CD increases in neonates with maturation during both active and quiet sleep (Scher et al. 2005) (Pereda et al. 2006) (Janjarasjitt et al. 2008). Non-linear methods also have been used to assess

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interdependences between EEG signals within different brain regions in both neonates (Pereda et al. 2001). De la Cruz et al (2007) recently reported that both linear and non-linear interdependences coexist in the term infant while exclusively non-linear relationships exist in the preterm infant.

We recognize that our study cohort was small. Repeated assessments with a larger sample size are required, including equal numbers of subjects of each gender and with similar ranges of birthweights. Moreover, our study did not examine sleep measures when the infants were not receiving SSC. Therefore, the degree to which sleep changes carryover to non-SSC periods is unknown. However, our results are provocative because of the highly significant results in the same direction, supporting the conclusion that accelerated neurophysiologic maturation may occur in the SSC cohort. This is also supported by our discriminant analyses. Secondly, no contemporaneous controls were obtained. Historical controls certainly introduce bias, although the recording conditions for both SSC and non-SSC cohorts were the same in both study protocols based on feeding, recording parameters and environmental aspects in similar level III neonatal intensive care units. Also, this is only a preliminary study in preparation for more expanded testing and analyses with contemporaneous control cohorts. Thirdly, the neurophysiologist scoring the pilot studies was not blinded to the knowledge that SSC had been the pilot group at term age. Fourthly, EEG-sleep segments were scored without knowledge of pretest or test conditions. Lastly, neonatal cohorts with varying severities of illness who receive SSC were not tested since altered or injured brain circuitries may respond differently to developmental care intervention.

CONCLUSION

The developmental care practice of SSC alters neonatal EEG-sleep organization with accelerated maturation. SSC practices in the neonatal intensive care unit may have an important impact when administered over an extended period on brain maturation involving multiple interconnected neuronal pathways as assessed by computer analyses of EEG-sleep measures.

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Table 1

Subject Summary

	SSC	Non-SSC (PT)	Non-SSC (FT)
Number of subjects	8	78	48
Sex			
Female	2	37	27
Male	6	41	21
Race			
Caucasian	5	44	33
African American	2	29	13
Other	1	5	2
Birth Data			
Gestational Age (wks)	30.6 ± 0.7	29.5 ± 1.9	40.2 ± 1.4
Birth Weight (kg)	1.52 ± 0.20	1.19 ± 0.21	3.59 ± 0.49
Study Data			
Day of Life	72.3 ± 2.7	79.5 ± 19.9	5.3 ± 10.0
Study Postmenstrual age (wks)	40.8 ± 0.6	40.8 ± 2.0	41.0 ± 1.5
Study Weight (kg)	3.49 ± 0.47	3.28 ± 0.81	3.58 ± 0.55

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Table 2A

Summary of EEG-Sleep Comparisons

	SSC	Non-SSC (PT)	Non-SSC (FT)
Left/Right Correlation Index	0.13 ± 0.10	0.16 ± 0.08	0.11 ± 0.03
REM Index	0.96 ± 0.61	4.49 ± 2.47*	6.66 ± 4.12*
Quiet Sleep %	46.3 ± 9.0	36.2 ± 8.0*	34.2 ± 7.4*
Respiratory Ratio Index	0.73 ± 0.05	0.75 ± 0.05	0.77 ± 0.04*
Sleep Cycle Length (minutes)	71.0 ± 13.2	70.0 ± 18.7	58.9 ± 14.3*
Spectral Index	−6.84 ± 0.40	−6.94 ± 0.62	−6.51 ± 0.44*
Arousal Index	2.96 ± 0.99	1.41 ± 1.14*	3.02 ± 1.79

*significant difference from SSC

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Table 2B

Summary of Complexity Measures

	Approximate Entropy			Sample Entropy		
Electrode Pair	**SSC**	**Non-SSC (PT)**	**Non-SSC (FT)**	**SSC**	**Non-SSC (PT)**	**Non-SSC (FT)**
T3-O1	0.84 ± 0.29	0.90 ± 0.24	0.97 ± 0.23	0.99 ± 0.29	1.13 ± 0.24	1.20 ± 0.23
T4-O2	0.86 ± 0.28	0.84 ± 0.27	0.88 ± 0.29	1.01 ± 0.28	1.00 ± 0.27	1.02 ± 0.29
C3-O1	0.84 ± 0.31	0.97 ± 0.22	0.98 ± 0.25	0.99 ± 0.31	1.20 ± 0.22	1.20 ± 0.25
C4-O2	0.88 ± 0.28	0.85 ± 0.31	0.84 ± 0.32	1.03 ± 0.28	1.01 ± 0.31	0.99 ± 0.32
T3-C3	0.90 ± 0.35	0.93 ± 0.24	0.94 ± 0.28	1.06 ± 0.35	1.12 ± 0.24	1.12 ± 0.28
C3-Cz	0.95 ± 0.37	0.88 ± 0.29	0.98 ± 0.27	1.10 ± 0.37	1.03 ± 0.29	1.14 ± 0.27
Cz-C4	0.94 ± 0.34	0.76 ± 0.37	0.87 ± 0.35	1.09 ± 0.34	0.90 ± 0.37	1.03 ± 0.35
C4-T4	0.90 ± 0.32	0.81 ± 0.29	0.81 ± 0.37	1.06 ± 0.32	0.97 ± 0.29	0.94 ± 0.37

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Table 3

Discriminant analysis using the Mahalanobis metric.
Mean Mahalanobis Distance Between Neonates at 40-41 Week and the Pittsburgh Controls using Complexity Measures.

	Approximate Entropy		Sample Entropy	
SSC	Non-SSC		Non-SSC	
Neonate Number	Full term	Preterm	Full term	Preterm
1	4.33	5.47	3.07	4.20
2	2.90	3.27	2.12	2.57
3	2.22	3.45	1.71	2.75
4	2.73	4.50	2.13	3.65
5	2.85	4.71	2.27	3.94
6	2.64	3.53	2.10	2.90
7	2.49	4.64	1.95	3.72
8	2.96	4.67	2.23	3.81
Mean Distance	2.90	4.32	2.20	3.48
Standard Dev.	0.59	0.74	0.37	0.58