Neurophysiologic Assessment of Brain Maturation: Preliminary results of a six-week trial of skin contact with preterm infants

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Statement of Problem:

Neurophysiologic studies of neonatal state over the last 50 years have demonstrated transitions that are important for assessing functional brain organization and maturation during a time interval of rapid growth and development. Beyond the usefulness of these studies to assess neonatal encephalopathy following acute illness, physiologic studies provide serial assessments of multiple interrelated brain functions during the premature infant's convalescence, sometimes over many months. Given the increasing incidence of premature infants born in the United States, greater emphasis on developmentally sensitive care paths by nurses and physicians need to be discussed. Practices as skin-to-skin contact (SSC) are employed to promote physiological stability and interaction between parents and their infants. Validation of this specific developmental care practice with neurophysiologic studies was the objective of this pilot study, in preparation for a larger scale investigation of SSC's effects on brain maturation with consequences for later neurodevelopment. We predict that combined linear and non-linear signal measures can distinguish neurodevelopment in neonates with SSC who are altered in brain maturity compared with non-SSC groups.

Statement of Program and Study Design:

Our multi-center neonatal sleep consortium has collected data over 16 years from 3 obstetrical-neonatal centers, demonstrating the ability to investigate EEG-sleep in neonatal populations using computational models. We have investigated sleep ontogeny and its relationship to neurodevelopment for 150 healthy neonates without postnatal illnesses (NS0111 0 and NS26793) as well as 221 medically high-risk neonates (RROO084, NS34508, NR01894). We recently completed a study of EEG-sleep studies (N=75) with respect to SSC (NR04926). Over 1062 multi-hour EEG-sleep studies have been digitally stored and are available for analyses. Each record is visually analyzed to identify neonatal sleep state, arousals, REMs and body movements, based on 18 polygraphic channels. Sampling rates, filtering strategies and mathematical algorithms will be discussed. This pilot study involved 16 EEG sleep studies on 8 neonates who were serially studied at 32 and 40 weeks corrected age. Each child had received a daily five-hour session ofSSC. Comparisons of brain organization and maturation measures of this pilOt "group with the previous study cohorts of preterm and fullterm neonates who did not receive SSC were performed. Linear and non-linear signal measures were used to compare groups. Linear measures consisted of seven representative physiologic behaviors grouped as a dysmaturity index (DJ) that can differentiate preterm and fullterm cohorts at similar corrected ages (Scher, 1997; 2003). The seven measures are numbers of RE Ms, numbers of arousals during quiet sleep, percentage of quiet sleep, sleep cycle length, spectral beta power, spectral correlation, and respiratory regularity. The Mahalanobis Distance (MD) was used to calculate the capital DJ for each child. MD calculates the differences in the preterm vector to the center of the cluster of fullterm infants

at the same corrected age. Fullterm infants tend to cluster fairly tightly around a location that depends on corrected age, gender and race. Preterm infants are dispersed and center around a
different location, based on maternal, fetal, placental and neonatal factors. Two non-linear time series analysis techniques were chosen to compare 8 EEG channels, approximate entropy and sample entropy, based on an earlier study demonstrating significant differences in brain complexity (correlation dimension) with increasing corrected ages up to term as well as between preterm and fullterm cohorts at term age (Scher et aI., 2005).

Summary of Results:

Significant differences in five linear measures distinguish the SSC from the non-SSC cohorts, based on two sample T -test comparisons. The SSC cohort at corrected term ages exhibited fewer numbers ofREMs (p=.OOOl), higher percentages of quiet sleep (p=.0005), increased respiratory regularity (p=.OO77), longer sleep cycle length (p=.0148), and less spectral beta (p=.0259), when compared with fullterm cohorts. The SSC cohort exhibited fewer rems (p=6.4 7 E-05), greater arousal numbers (p=.0002), higher percentage of quiet sleep (p=.0005), and greater spectral beta (p=.0136), when compared with the preterm cohort corrected to term age who did not receive SSC.

Significant differences for one of the two non-linear measures (sample entropy) using two sample T-test comparisons ($p<.05$) distinguish the SSC from the non-SSC cohorts. Five brain regions were assessed to have greater complexity for the SSC cohort as compared with the non-SSC preterm cohort at term age (C4-02, T4-02, T4-C4, C3-Cz, and C4-Cz), while three of these five regions were more complex than both fullterm and preterm cohorts at term (C4-02, T4-C4, C4-Cz). Brain regions corresponding to the left posterior quadrant were less complex than other regions for the SSC group compared with either non-SSC cohort (T3-C3, C3-01, T3-01).

Implications and Future Studies:

Combined linear and non-linear signal measures distinguish functional brain organization and maturation in neonates. These findings supplement an initial study which demonstrated fewer arousals and more quiet sleep after a single SSC session at 32 weeks gestation (Ludington-Hoe et aI., 2006). This pilot study suggests that the SSC cohort exhibits more advanced brain function than both non-SSC preterm at term and fullterm cohorts, when SSC was provided daily over a 6-week period. This accelerated maturational trend was region-specific to the right hemisphere, bilateral parasagittal regions and brain stem/diencephalic regions, but not involving the posterior quadrant of the left hemisphere. Limited one or two channel cerebral functioning monitoring devices would not document differences between hemispheres since the electrodes are confined to the parasagittal regions.

Our consortium's overall objective is to apply computer analyses of state as phenotypic markers of developmental neural plasticity, to provide a more complete picture of how adaptation and remodeling relate to physiologic function and brain development of the neonate, infant and child. Clinical applications can be achieved using computational phenotypes that incorporate linear-stochastic as well as non-linear deterministic features that either predict and/or detect temporal patterns or novel events that have clinical relevance during acute and convalescent care. Such events include detection of state transitions, abnormal seizure states, abnormal encephalopathic states, environmental interventions, drug treatment protocols and maturational trends to predict

outcome. Data sets derived from computational phenotypes can also be compared with other diagnostic modalities for both clinical care and research applications, including quantitative neuroimaging data sets, neuropsychological testing results, and genetic polymorphisms associated with disease risk.

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