Electroencephalographic activity of preterm infants is increased by Family Nurture Intervention: A randomized controlled trial in the NICU

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Objective: To assess the impact of Family Nurture Intervention (FNI) on electroencephalogram (EEG) activity in preterm infants (26–34 weeks gestation).

Methods: Two groups were tested in a single, level IV neonatal intensive care unit (NICU; standard care or standard care plus FNI) using a randomized controlled trial design. The intervention consists of sessions designed to achieve mutual calm and promote communication of affect between infants and their mothers throughout the NICU stay. EEG recordings were obtained from 134 infants during sleep at 35 and 40 weeks postmenstrual age (PMA). Regional brain activity (power) was computed for 10 frequency bands between 1 and 48 Hz in each of 125 electrodes.

Results: Near to term age, compared to standard care infants, FNI infants showed robust increases in EEG power in the frontal polar region at frequencies 10 to 48 Hz (20% to 36% with \( p \)-values <0.0004). Effects were significant in both quiet and active sleep, regardless of gender, singleton-twin status, gestational age (26–30 or 30–35 weeks) or birth weight (<1500 or >1500 g).

Conclusion: FNI leads to increased frontal brain activity during sleep, which other investigators find predictive of better neurobehavioral outcomes.

Significance: FNI may be a practicable means of improving outcomes in preterm infants.

1. Introduction

Preterm birth at <37 weeks gestational age (GA) in the United States has an incidence of 12% (Hamilton et al., 2013). The problem addressed by this current study is that accompanying early preterm birth is a period of prolonged physical and emotional separation of mothers and infants during neonatal care with increased risk for adverse outcomes during subsequent growth and development. This vulnerability manifests as neurobehavioral disorders that include attention deficits (Johnson and Marlow, 2013).
executive dysfunction (Baron et al., 2012; Peterson et al., 2000), depression and psychotic disorders (Nosarti et al., 2012), and autism spectrum disorder (Pinto-Martin et al., 2011). Numerous preclinical and clinical studies over the course of the past fifty years have confirmed that early mother-infant separation leads to a wide array of adverse physiological and behavioral consequences that persist throughout life (Coe et al., 1988; Hofer, 1996; Sanchez et al., 2001). However, other preclinical studies indicate that increasing mother/infant interactions, such as buffered stress responses, can have positive effects on outcome (MeaneY et al., 1996). Over the past two decades, specific interventions directed at premature infant care in Neonatal Intensive Care Units (NICU), such as Newborn Developmental Care and Assessment Program (NIDCAP) (Als et al., 1994, 2012), skin-to-skin care (Conde-Agudelo et al., 2011, Feldman et al., 2002) and massage therapy (Field et al., 2006, 2010, Vickers et al., 2004), have shown significant effects on outcomes. However, these interventions are not universally accepted and further studies are necessary to document efficacy in preterm infants (Conde-Agudelo et al., 2011, Ohlsson and Jacobs, 2013).

This research study tests a new approach for improving development of preterm infants, Family Nurture Intervention (FNI). The distinguishing feature of FNI is that the intervention staff facilitates communication of affect and physiologic co-regulation between mother and infant. The intervention starts early and continues over the full course of hospitalization, thereby minimizing the effects of mother–infant separation in the Neonatal Intensive Care Unit (NICU). The intervention includes mother and infant scent cloth exchange, sustained touch and vocal soothing in the isolette with eye contact, wrapped skin-to-skin holding and family-based support sessions (Welch et al., 2012) (see Methods below).

FNI was based both on a method used to treat emotional, behavioral and developmental disorders in older children (Welch et al., 2006) and on basic research in animal models that revealed sensorimotor, olfactory and nurture-based activities within normal mother–infant relationships (Hofer, 1975, 1994, 1996; Myers et al., 1989a,b). In recent laboratory studies, central neural mechanisms have been found for these effects, involving epigenetic regulation of gene expression patterns in specific brain regions, from infancy to adulthood, as a result of variations in early mother-infant interactions (MeaneY et al., 1996; MeaneY, 2001; Jensen and Champagne, 2012; Zhang et al., 2013; Calджi et al., 2011). FNI can be safely and feasibly implemented in a level IV NICU without any negative impact on length of stay (Welch et al., 2013).

Quantitative characterization of features of the EEG unique to early development provides state-dependent indices for tracking changes in specific neurophysiological mechanisms critical for normal development of cortical function (Grieve et al., 2005, 2007, 2008; Isler et al., 2005; Myers et al., 1997, 1993, 2012; Sahni et al., 1995, 2005). The impact of prior NICU interventions on brain development has been assessed using electroencephalogram (EEG) measures of complexity and coherence of brain activity during sleep (Als et al., 2012; Kaffashi et al., 2012; Ludington-Hoe et al., 2006). Prior studies have found that preterm infants suffer from functional abnormalities mediated by the frontal cortex, including attention, emotion regulation, language and cognition (Baron et al., 2012; Johnson and Marlow, 2011; Nosarti et al., 2012; Peterson et al., 2000; Pinto-Martin et al., 2011). Other studies have found that activity (power) at higher frequencies measured during sleep in preterm and term infants is predictive of Bayley neurobehavioral scores later in development (Scher et al., 1996). This current study obtained high-density, 124-lead, EEG recordings as a novel means to assess changes in brain activity from a NICU intervention. The current findings show near term age that the FNI group shows highly significant increases in EEG power in high frequency bands in the frontal cortex.

2. Methods

2.1. FNI trial design

Data for this study were obtained in a single-center, parallel group, randomized controlled trial (RCT) in the level IV NICU at Morgan Stanley Children’s Hospital of New York at Columbia University Medical Center. ClinicalTrials.gov has registered this trial (#NCT01439269). Columbia University Medical Center Institutional Review Board approved all recruitment, consent, and study procedures. The target enrollment for this study was 150 infants. The original protocol restricted the gestational ages of the infants to 26 to 32 weeks 6 days. After eight months of enrollment, we obtained approval to increase the age to 34 weeks 6 days in order to increase the rate of enrollment, but the target enrollment of 150 infants was not changed. Excluded were mothers that did not understand and speak English, or had a history of drug addiction or severe mental illness. Entry into the study required that families have at least one adult other than the mother in the home. Excluded infants were those with a birth weight below the third percentile for gestational age or significant congenital defects. Shown in the consort chart (Supplementary Figure S1) are the number of eligible infants and consents obtained.

2.2. FNI activities and procedures

Following consent, mothers assigned to the FNI group met with Nurture Specialists who worked with the mothers and their families throughout the study to facilitate all aspects of the intervention. Mothers of infants assigned to the SC condition received the care that is standard for infants admitted to the NICU. The timeline of the intervention and the sequence of mother-infant interactions are depicted in Fig. 1.

The first FNI activities took place with the infant confined to the isolette. As soon as possible after birth, the mothers started reciprocal scent cloth exchanges. Two small cotton scent cloths were given to the mothers, one to wear in their bra and the other to place under the head of their infant. Mothers were encouraged to repeat this cycle at each visit to the NICU. As infants became more stable, Nurture Specialists facilitated FNI mothers in making affective contact with their infants through the ports of the isolette, using firm and sustained touch and ‘containment’, speaking emotionally to their infants in their native language and when possible, making eye contact. When infants were medically able to leave the incubator, Nurture Specialists helped FNI mothers to engage in skin-to-skin, or non-skin-to-skin holding to continue vocal soothing and eye to eye contact. Mothers were facilitated in engaging regularly in these activities for a minimum of 1 h at a time. When family members were available, the Nurture Specialist

![Fig. 1. FNI Timeline](image-url)
engaged them in sessions that discussed the importance of the FNI activities between mother and infant, and offered support to the families with ongoing problems and with their needs arising from the arrival of their new infant.

2.3. EEG acquisition and sleep state coding

EEG recording used 128-electrode data acquisition systems (EGI, Inc., Eugene, Oregon); however, only 124 leads are used in infants. Data were obtained between 11 am and 4 pm within ~30 min after a normally scheduled feeding. A study session of ~90 min duration was required to acquire ~60 min of EEG data. The details of EEG acquisition are described in prior work (Grieve et al., 2008) Following consultation with the manufacturer of the EEG system, we used special methods to maintain electrode/scalp contact, including covering the electrode net with plastic wrap to diminish evaporation of the saline in the electrode sponges and covering the net and plastic wrap with an elastic material (Surgi- last). Application of the net and these extra measures usually took about 5 min. These procedures generally allowed impedances to be kept below 50 kohms per manufacturer’s recommendation. The EEG was sampled at 1000 samples/s using a vertex reference. The voltage from each lead was band-pass filtered from 0.1 to 400 Hz and then digitized with 16 bits per sample at the rate of 1000 samples/second. Then, in software, data were re-referenced to the average of the 124 lead EEG montage and processed to obtain measures of power ($\mu$V$^2$) at specific frequencies for each electrode. The negative of the average reference approximates the voltage at the vertex lead as referenced to a point at infinity, thus producing the 125th lead.

Research assistants performed visual coding of quiet and active sleep, indeterminate, awake and crying states once each minute. This coding was done continuously throughout the EEG study with behavioral criteria previously shown to be appropriate for preterm infants (Stefanski et al., 1984).

2.4. EEG signal artifact rejection

Multiple steps were taken to diminish inclusion of EEG data contaminated by movement-related or other sources of non-cortical electrical activity. The standard deviation of voltage was computed for each 30-s epoch of each lead. Individual lead data were excluded if the standard deviation of the lead exceeded 50 $\mu$V. Epochs were excluded if more than 20 of the 125 leads exceeded the standard deviation criterion and entire studies were excluded if more than 80% of their epochs were excluded.

2.5. EEG power analysis, outlier rejection and statistical analyses

After dropping all defined artifacts, data were available from at least one EEG study for each of 134 infants (63 SC, 71 FNI). From these data, EEG power was computed using 1 s FFTs for each of the 125 leads. Average power for each of 10 frequency bands (1–3, 3–6, 6–9, 9–12, 12–15, 15–18, 18–21, 22–24, 25–36 and 37–48 Hz) was computed for 30-s epochs throughout the session.

To define outliers in the power data, regression analyses of log power versus PMA at the time of the recording were conducted for each lead, frequency band and sleep state (2500 total analyses; 125 leads $\times$ 10 bands $\times$ 2 states). Outliers from the regression line were defined when residuals with Studentized value exceeded 1.98 (i.e. $p \sim 0.05$ with df $\sim 300$). These values were set to zero. Finally, muscle activity can contribute to outlier values of power in a lead at nearly all frequencies. As a percentage of EEG power in a band, these outliers are larger in high frequency bands (Shackman et al., 2009). Accordingly, to limit the contribution of muscle activity, if data from a lead were set to missing because of excessive power in the highest frequency band (37–48 Hz), then data for all frequency bands for that lead were set to missing.

With elimination of outliers and acceptance of a minimum of 3 min of EEG data within each sleep state to increase the stability of measures of EEG power, the median power for all epochs of active sleep and quiet sleep for each lead and frequency band was determined. This allowed the inclusion of 293 early and near term studies (129 SC, 164 FNI) for AS analyses and 290 early and late term studies (127 SC, 163 FNI) in the QS analyses. In both AS and QS, there was a trend for a greater fraction of SC studies to be excluded as compared with the fraction of FNI studies that were excluded. However, in neither state were these group differences in exclusions significantly different (AS: $X^2 = 2.52$, $p = 0.11$; QS: $X^2 = 3.04$, $p = 0.08$).

EEG studies were divided into 2 age groups; preterm age (33.8–36.9 weeks PMA) and a near term age (37.2–44.4 weeks PMA). 80% of the preterm age studies and 25% of the near term age studies were conducted in the NICU. The remaining studies were done in the follow-up clinic. These percentages did not differ between the study groups. For overall descriptive purposes, the first phase of the analyses performed t-tests to characterize differences between FNI and SC for each lead, for each frequency band, for each sleep state, and for each of the two study ages.

To determine whether group differences were statistically significant, ANOVAs of log EEG power for each study age group were conducted for each of the five regions (frontal polar, frontal, temporal, parietal, occipital) (Fig. 2) for each of the 10 frequency bands and for each sleep state. These analyses had one between-subjects factor (FNI vs. SC) and one within-subjects factor (left hemisphere, right hemisphere). Gestational age at birth and PMA at the time of the EEG studies were included as covariates.

When a given subject had more than one study within an age range, results were averaged over the multiple studies within that range. Approximately one third of the infants had multiple studies within the early range and another third within the near to term age range. The distribution of multiple versus single studies was not significantly different between the two groups.

![Fig. 2. Schematic of high density EEG net. The 124 electrodes in the EEG net are distributed within ten standard brain regions for the regional analyses of the study. Note 10 midline leads (open circles) were excluded from statistical analyses by region.](image-url)
Within each age group 100 tests were conducted (10 frequency bands × 5 regions × 2 sleep states), producing p-values that reflected the main effects of treatment. To control for multiple testing, we employed the False Discovery Rate procedure (Benjamini and Hochberg, 1995) with a threshold set at 10%. We performed additional analyses on subsets of infants with EEG studies who had EEG studies at both ages (33 SC, 43 FNI). These were group by repeated measures (age) ANOVAs and were limited to left frontal polar power in the 19–21 Hz band.

3. Results

3.1. Demographics and clinical characteristics

There were no significant differences between SC and FNI groups with regard to parent demographics, maternal or infant birth or clinical conditions (Supplementary Tables S1–S3).

3.2. EEG study characteristics

One hundred thirty-four infants (63 SC, 71 FNI) from 105 (51 SC, 54 FNI) pregnancies including singletons and twins provided EEG data for these analyses (Supplementary Table S4). The recordings were 1 h in duration in both study groups and in both age groups. In the early EEG studies, FNI infants had fewer epochs identified as outliers in both active sleep (AS) and quiet sleep (QS) states than did SC infants.

3.3. Electrode by electrode differences in EEG power at the two age ranges

To evaluate the effect of FNI on EEG power, we conducted t-tests for each electrode, within each sleep state and PMA range and for each of 10 frequency bands. Electrode maps of the p-values from these t-tests are shown in Fig. 3 for quiet sleep and in Fig. 4 for active sleep. Included in the maps are data for each of 10 frequency bands across the spectral range from 1 to 48 Hz for both the early and near term studies. Results obtained at the near to term age range indicate there were highly significant effects of the intervention (red to dark brown electrodes, lower sets of electrodes in Figs 3 and 4). In both sleep states, the intervention led to regional increases in power, particularly in the most frontal electrodes at frequencies above 10 Hz. At the early study age range, there were no robust differences in power between the two groups.

3.4. Regional effects of FNI on EEG power

To test whether the individual electrode differences in Figs 3 and 4 were regionally significant, we conducted a series of ANOVAs in which the main effect of FNI vs. SC was determined across ten regions (Fig. 2), ten frequency bands, two sleep states, and both age ranges. Data from left and right hemispheres were included as a within-subjects factor in these analyses and gestational age at birth and PMA at the time of EEG study were covariates.

ANOVA found no significant intervention group by hemisphere interactions (Supplementary Tables S5–S8). Thus, results only focus on the main effect of intervention group. Identification of the subset of p-values that passed the 10% False Discovery Rate threshold revealed that near to term age, power above 10 Hz in the leads over the frontal polar cortex was significantly affected by the intervention. As shown in Table 1, there was increased power in this region in FNI infants that ranged from 19% to 36% greater than that in SC infants. The effects of FNI appeared to be more pronounced in QS, although robust changes were found in both sleep states. At frequencies above 10 Hz, seven of the QS and six of the AS ANOVA tests passed the 10% FDR threshold.

3.5. FNI increased EEG power in both the first and second half of study period

To test whether the effects of FNI were consistent over the course of the trial, we divided the data into the first half and second half of the study period for enrollment in the RCT. We focused on the data obtained at near to term age in QS. Although multiple
frequency bands showed highly significant differences, we focused on the band that had the most robust results (19–21 Hz). Inspection of the electrode by electrode results in Figs. 3 and 4 suggested somewhat more robust results on the left side. Thus, we conducted these post hoc tests using data from the left frontal polar region. An ANOVA for effects of group (FNI vs. SC) and study period half showed there was a highly significant difference between groups with FNI greater than SC (F(1, 92) = 20.06, p < 0.00003), but no significant group by study half interaction (p = 0.99). Post-hoc t-tests showed a significant effect of group in both halves of the intervention (p < 0.007 (SC/FNI, n = 24/26) and p < 0.001 (n = 21/27), respectively).

3.6. FNI increased EEG power in both males and females

A gender by group comparison determined whether the effects of FNI treatment on EEG power were similar in males and females. The ANOVA showed a robust main effect of group with FNI greater than SC (F(1, 92) = 20.17, p < 0.00003), but no significant interaction between group and sex (p = 0.60). The mean power for males and females in each group is shown (Fig. 5A). Post-hoc t-tests showed a significant effect of FNI in both males and females (p < 0.001 (SC/FNI, n = 20/28) and p < 0.007 (n = 25/25), respectively).

3.7. FNI increased EEG power in both singletons and twins

We also conducted an ANOVA to determine if the effects of FNI were similar in singletons and twins (Fig. 5B). There was a highly significant effect of group with FNI greater than SC (F(1, 92) = 21.19, p < 0.00002) but there was also a significant interaction between twin/singleton status and group (F(1, 92) = 6.18, p < 0.02). Post-hoc tests showed that the effects of FNI were significant in both singletons and twins (p < 0.03 (SC/FNI, n = 27/29) and p < 0.01 (n = 18/24), respectively).

3.8. FNI increased EEG power independent of age or weight at birth

Next, we divided the infants into two groups based on gestational age at birth. There were 28 infants born ≤30 weeks (12 SC, 16 FNI) and 70 infants born >30 weeks (33 SC, 37 FNI). There was a significant main effect of age group with FNI greater than SC (F(1, 94) = 14.43, p < 0.0003) but no significant interaction between intervention group and birth age group (p = 0.48). The mean power for each birth age group is shown in Fig. 5C. Post-hoc t-tests showed there was significantly greater power in the FNI group in both age groups (≤30 weeks PMA, p < 0.03; >30 weeks PMA, p < 0.001). The effect of the intervention in the left frontal polar region at 19–21 Hz was also significant for infants born <1500 g (p < 0.005 (SC/FNI, n = 18/32)) as well as infants born ≥1500 g (p < 0.001 (n = 27/21)) with greater power in the FNI group.

Table 1

Results from analyses of Frontal Polar EEG power from the near to term studies (PMA 37–44.4 weeks). For each sleep state (active and quiet) analyses were repeated measures ANOVAs of log EEG power for each of 10 frequency bands. These analyses had one between subjects factor (Group: FNI vs. SC) and one within subjects factor (hemisphere). The p-values shown are for the main effect by Group. Note the number of subjects across frequency bands and states was not constant because outliers were set to missing for individual cells in these analyses. There were no significant interactions between treatment group and hemisphere. In both quiet and active sleep in all frequency bands, the power was greater in FNI than in SC infants. Presented in bold are the p-values which passed a 10% False Discovery Rate threshold based on p-values from 200 tests (5 regions × 10 frequency bands × 2 ages × 2 states).

<table>
<thead>
<tr>
<th>Frequency band (Hz)</th>
<th>Quiet sleep (FNI vs. SC (%))</th>
<th>p (Group Ns)</th>
<th>Active sleep (FNI vs. SC (%))</th>
<th>p (Group Ns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>+8</td>
<td>0.26438 (44/51)</td>
<td>+11</td>
<td>0.19612 (44/50)</td>
</tr>
<tr>
<td>4–6</td>
<td>+16</td>
<td>0.07690 (44/53)</td>
<td>+5</td>
<td>0.38996 (44/50)</td>
</tr>
<tr>
<td>7–9</td>
<td>+19</td>
<td>0.03022 (44/52)</td>
<td>+12</td>
<td>0.10840 (44/50)</td>
</tr>
<tr>
<td>10–12</td>
<td>+21</td>
<td>0.00364 (44/53)</td>
<td>+20</td>
<td>0.00360 (44/51)</td>
</tr>
<tr>
<td>13–15</td>
<td>+21</td>
<td>0.00501 (44/50)</td>
<td>+20</td>
<td>0.00459 (44/49)</td>
</tr>
<tr>
<td>16–18</td>
<td>+30</td>
<td>0.00018 (44/52)</td>
<td>+20</td>
<td>0.00351 (44/50)</td>
</tr>
<tr>
<td>19–21</td>
<td>+32</td>
<td>0.00003 (44/52)</td>
<td>+19</td>
<td>0.00375 (44/49)</td>
</tr>
<tr>
<td>22–24</td>
<td>+32</td>
<td>0.00006 (44/52)</td>
<td>+20</td>
<td>0.00525 (44/49)</td>
</tr>
<tr>
<td>25–36</td>
<td>+36</td>
<td>0.00007 (44/53)</td>
<td>+23</td>
<td>0.00307 (44/51)</td>
</tr>
<tr>
<td>37–48</td>
<td>+31</td>
<td>0.00121 (44/53)</td>
<td>+20</td>
<td>0.01474 (44/51)</td>
</tr>
</tbody>
</table>

Fig. 4. EEG power during active sleep. In active sleep FNI had effects on EEG power at the older age range (after ~6 weeks of FNI) but not the early range. These effects were most apparent in frontal regions. Shown are electrode maps of the p-value for the differences in power between FNI and SC infants in t-tests for each electrode, across the spectral frequency range from 1 to 48 Hz and PMA range for each of 10 frequency bands across all 30 s epochs that were behaviorally coded as active sleep.
3.9. FNI increased EEG power independent of testing before or after discharge

The majority of near to term EEG studies were conducted post-discharge in our follow-up clinic (34 SC, 34 FNI) while a few were obtained in the NICU prior to discharge (10 SC, 12 FNI). Analyses showed a main effect of group with FNI greater than SC ($F(1, 86) = 14.54, \ p < 0.0003$) but no significant interaction between group and discharge status ($p = 0.56$) (Fig. 5D). Moreover, there was a significant effect of FNI in both of these subsets (tested in NICU $p < 0.02$; tested in follow-up clinic $p < 0.001$).

3.10. FNI alters developmental trajectories of EEG power

Next, we examined developmental trajectories of EEG power by analyzing changes in power with age (controlling for gestational age at birth and PMA at testing). Repeated measures ANOVAs were conducted using data from subjects with measurements both early at 33.8–36.9 PMA and near-term at 37.2–44.4 PMA (43 FNI, 33 SC). The developmental trajectories for EEG power in the 19–21 Hz band during QS for the left and right sides of five brain regions are shown in Fig. 6. Results showed that left frontal polar power increased in FNI infants with PMA, whereas SC infants showed no significant change with PMA (Fig. 6A). This pattern of change with age resulted in a significant age by group interaction ($p < 0.0001$). A significant age by group interaction was also found for right frontal polar power ($p < 0.001$). Even though the differences in frontal power at term age were not significant, the change from the early PMA studies to the near to term age studies was greater in FNI infants in PMA, whereas SC infants showed no significant change with PMA (Fig. 6B). A significant age by group interaction was also found for the left temporal ($p < 0.03$; Fig. 6C), as well as for the left and right parietal regions ($p < 0.008, p < 0.005$, respectively; Fig. 6D), and for the right occipital region ($p < 0.01$; Fig. 6E). Post-hoc tests showed that power increased significantly ($p < 0.02$ to $p < 0.00001$) in FNI in all but the left temporal region.

In contrast, power increased in SC infants only in the left occipital region ($p < 0.05$). Moreover, in SC, EEG power in the left frontal region decreased with age ($p < 0.02$).

4. Discussion

Preterm infants are a growing segment of the population. These infants are taken from their uterine environment before fetal development is complete and are exposed to an artificial environment. Advances in technology have made it possible to reduce mortality at early gestational ages. However, adverse outcomes in preterm infants remain high.

There are several reports of positive impact of non-medical interventions on outcomes following neonatal intensive care (Als et al., 1994, 2012, Conde-Agudelo et al., 2011, Feldman et al., 2002, 2006, 2010, Vickers et al., 2004), although comprehensive assessments of these interventions suggest that they have limited usefulness in resolving problems of long-term outcome (Ohlsson and Jacobs, 2013, Symington and Pinelli, 2006). The Newborn Individualized Developmental Care and Assessment Program (NIDCAP) focuses on providing care of NICU infants tailored to their observed neurobehavioral characteristics (Als et al., 1994). NIDCAP results in improved medical and neurobehavioral outcomes (Als et al., 2004; Buehler et al., 1995; McAnulty et al., 2009). These effects are correlated with MRI- and EEG-based evidence of increased connectivity between frontal and occipital brain regions following NIDCAP intervention (Als et al., 2004). Encouraging mothers to engage in skin-to-skin care of their preterm infants has positive effects upon growth and clinical course in the NICU (Conde-Agudelo et al., 2011), as well as longer term neurobehavioral outcomes (Feldman et al., 2002). Skin-to-skin care has also been reported to increase EEG-based measures of complexity, interpreted as enhanced maturation of brain function (Kaffashi et al., 2012; Scher et al., 2009). Massage intervention in preterm infants has been shown to increase growth rates and reduce length of stay in the NICU (Field et al., 2010; Field et al., 2008, Vickers et al., 2004). Two reports...
from a small trial (N = 10/group) found that massage therapy accelerated developmental decreases in inter-burst intervals in EEG activity, shortened latencies in visual evoked responses, and caused a transient enhancement of visual acuity at three months of age (Guzzetta et al., 2009, 2011). These studies also showed that massage therapy led to higher levels of EEG power during active sleep.

Although FNI incorporates some aspects of the above interventions, it differs in central focus. FNI specifically facilitates the pairing of mother’s communication of emotion with exchange of scent, comforting touch, vocal soothing, holding and the experience of mutual calming. This pairing of affect communication and sensory interaction may underlie another mechanism that could explain the effects of FNI on brain function; namely, learning. The neural substrates for learning exist very early in development and have been demonstrated in early motor learning paradigms in rat fetuses (Robinson et al., 2008). Other studies have demonstrated that the human fetus learns to recognize the mother’s voice (DeCasper and Fifer, 1980; Fifer and Moon, 1994; Moon and Fifer, 2000) and scent (Marlier et al., 1997; Schaal et al., 2000). New learning from olfactory stimuli (Sullivan et al., 1986a,b) guides behavior during the early postnatal period, with temperature and touch being key determinants of affiliative learning (Kojima and Alberts, 2011). Learning in infants can occur during a wide range of circumstances, such as feeding (Delaunay-El Allam et al., 2006) and even during sleep (Fifer et al., 2010). Based on this body of early learning studies and on the design of our intervention, it seems

Fig. 6. Developmental trajectories of EEG power are altered by FNI. EEG power (log 19–21 Hz /uV^2/Hz; mean ± SE) for left and right sides of the (A) frontal polar, (B) frontal, (C) temporal, (D) parietal and (E) occipital brain regions recorded during quiet sleep for SC (circles/dashed line) and FNI (Square/solid line) infants measured between 34 and <37 weeks PMA vs. >37 to 44 weeks PMA. The p-values are from ANOVAs and reflect the significance level of the interaction between age and intervention group controlling for gestational age at birth and PMA at testing.
very likely that some form of learning may underlie the effects on brain development of infants following FNI.

Indeed, our results show that near to term age infants who receive facilitated FNI exhibit robust differences in brain activity (EEG power), when compared to infants receiving standard care. The increases in EEG power in FNI infants ranged from 19% to 36% in frequencies from 10 to 48 Hz. The greatest percent change (+36%) occurred during quiet sleep in the low gamma frequency range (25–36 Hz). These findings are particularly convincing because they were obtained in a large randomized controlled trial that employed fine grained high density EEG records with repeated measurements over early development, and held true regardless of gender, singleton or twin status, gestational age at birth, or birth weight. Further, they held for infants enrolled in the first or second half of the study, as well as for infants studied near to term age while still in the NICU or after discharge.

FNI exerts its most highly significant effects in the frontal polar regions at beta and low gamma frequencies. Results from other studies have shown that increased high frequency power predicts better developmental outcomes at later ages. Results from our prior study in term infants with cardiac anomalies showed a positive correlation between left frontal beta power, during sleep, and Bayley scores at 18 months (Williams et al., 2012). This is consistent with prior work in both term and preterm infants (Scher et al., 1996; Tarullo et al., 2012). In older awake infants, frontal gamma power, thought to be related to level of arousal and attention, was correlated with cognitive abilities (Benasich et al., 2008). Resting frontal EEG gamma power measured in awake infants at 16 months of age predicted language capabilities at 3 years of age (Gou et al., 2011). These studies support the hypothesis that the increases in high frequency power we demonstrated in preterm infants following FNI presage improved neurobehavioral outcomes at later stages of development.

Based on studies in older infants, one might have expected to find effects of FNI on the early development of EEG power left/right asymmetry in our subjects in the 7–9 Hz frequency range. These studies showed asymmetry in EEG power in frontal areas, particularly at frequencies between 6 and 9 Hz in association with maternal depression (Dawson et al., 1999a,b), responses to fearful stimuli (Diaz and Bell, 2012), orphanage rearing (McLaughlin et al., 2011), and quality of maternal care (Hane and Fox, 2006; Hane et al., 2010). In contrast to all of the prior published asymmetry work, our data was obtained during sleep. In our study, we did not find significant left/right group differences in power, or any group by hemisphere interactions in the 7–9 Hz band, in postmenstrual age group, sleep state, or brain region. It is possible that left/right differences will emerge at later ages, but we did not record EEG beyond the near to term age range or in the awake state.

Although we found that main developmental effects of FNI were localized to frontal polar power, we also found significant group-by-age interactions in multiple brain regions. These results suggest that there are widespread changes in developmental trajectories of brain activity that could be mediated by FNI. Since this study was limited to a specific age range during sleep, it is also conceivable that increases in EEG power might be seen in the FNI group in other brain regions and/or at earlier ages under other test conditions, such as during the awake state or following stimuli that evoke EEG responses.

It is important to note that the effects of FNI on infant brain activation occurred with an apparently small “dose” of the intervention. Scent cloth exchange was made approximately 2–3 times per week, and Vocal Soothing and Sustained Touch with Eye Contact sessions took place approximately three times per week. Skin to Skin Holding sessions took place an average of two times per week for at least one hour each time. In total, Nurture Specialist-facilitated intervention sessions occurred on average approximately 4 h per week. This relatively small amount of time spent in nurturing activities, however, may not be an accurate indicator of the intervention effect. In other words, dose and effect may not be directly correlated. Behavioral and emotional effects might have been sustained in both mother and infant beyond each session. Sensory stimulation and associated brain activation during early development can elicit cascades of hormone and neurochemical events that can shape infant brain development (Johnston et al., 2001; Kuhn and Schanberg, 1998; Park and Poo, 2013). Thus, in addition to learning mechanisms, we speculate that the increased brain activity we see following FNI may serve to shape activity-dependent aspects of brain development and plasticity. In replication studies we plan to adapt EEG-based measures (Clapp et al., 2012) to track changes in brain plasticity as both markers and mechanisms for the effects of FNI.

Our ongoing clinical research will assess the proximal physiological and behavioral effects of paired nurturing activities, and explore underlying developmental mechanisms. In follow-up of this study cohort extending to two years of age and longer, we will determine the effects of FNI on cognition, language, attention, and emotion regulation.

5. Conclusions

Family Nurture Intervention is a novel intervention strategy for the neonatal intensive care unit that pairs communication of affect and interactions designed to calm both mother and infant. Compared to the SC group, the FNI group showed robust increases in high frequency EEG brain power in the frontal polar region at near to term age. These effects were independent of gestational age or weight at birth, gender, twin status, or discharge status when assessed. Such region and frequency-specific increases have been shown by others to correlate with better neurodevelopment at later ages. Results from this study support the importance of early mother–infant nurture and of facilitating family nurture in the NICU and suggest that FNI may provide an effective and practicable approach to improving outcomes in preterm infants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2013.08.021.


