

REGULAR ARTICLE

Family Nurture Intervention in preterm infants alters frontal cortical functional connectivity assessed by EEG coherence

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ABSTRACT

Aim: To assess the impact of Family Nurture Intervention (FNI) on cortical function in preterm infants at term age.

Methods: Family Nurture Intervention is a NICU-based intervention designed to establish emotional connection between mothers and preterm infants. Infants born at 26–34 weeks postmenstrual age (PMA) were divided into two groups, standard care (SC, N = 49) and FNI (FNI, N = 56). Infants had EEG recordings of ~one hour duration with 124 lead nets between 37 and 44 weeks PMA. Coherence was measured between all pairs of electrodes in ten frequency bands. Data were summarised both within and between 12 regions during two sleep states (active, quiet).

Results: Coherence levels were negatively correlated with PMA age in both groups. As compared to SC infants, FNI infants showed significantly lower levels of EEG coherence (1–18 Hz) largely within and between frontal regions.

Conclusion: Coherence in FNI infants was decreased in regions where we previously found robust increases in EEG power. As coherence decreases with age, results suggest that FNI may accelerate brain maturation particularly in frontal brain regions, which have been shown in research by others to be involved in regulation of attention, cognition and emotion regulation; domains deficient in preterm infants.

INTRODUCTION

Improvements in care have decreased the mortality and morbidity of prematurely born infants. Yet, the nearly 500 000 preterm infants born each year remain vulnerable to a broad range of adverse developmental outcomes, including attention deficits, cognitive and language delays, executive dysfunction, autism spectrum disorder (1–3). The potential biological conditions underlying these adverse outcomes include risks associated with premature exposure to extra-uterine environmental conditions, as well as prior and postnatal medical conditions and treatments. In addition, risk may also be due to the effects of physical and emotional separation of infant and mother while in the neonatal intensive care unit (NICU) (4).

Several intervention studies have focused on improving quality of interactions between mothers and their preterm infants (5–7). Collectively, these studies show that

intervening during the course of hospitalisation or shortly after discharge is associated with improved mother–infant interactions. We recently completed a randomised-controlled trial of the Family Nurture Intervention (FNI) in the NICU, which was designed to enhance the emotional connectivity between prematurely born infants and their mothers (8,9). FNI differs from other NICU interventions in concept, implementation and goal. Our hypothesis is that infants in the NICU are socially isolated and are being adversely conditioned by periodic requisite disruptive pro-

Abbreviations

EEG, Electroencephalogram; FDR, False discovery rate; FNI, Family Nurture Intervention; NICU, Neonatal intensive care unit; PMA, Postmenstrual age; SC, Standard care.

Key notes

- This randomised-controlled trial of a NICU intervention facilitates emotional connection between mothers and preterm infants.
- Coherence in FNI infants was decreased in regions where we previously found robust increases in EEG power.
- As coherence decreases with age, these results are consistent with the conclusion that FNI promotes brain maturation.

cedures, and that such conditioning can result in maladaptive responses to social and environmental stress (10). Our goal is to counter-condition these effects of NICU experience through coregulatory maternal conditioning to establish mother/infant emotional connection with repeated calming sessions (8).

Initial published results demonstrated that FNI led to robust increases in EEG power at term age in the frontal polar region of the brain when compared to infants receiving standard care (SC) (11). This increase in EEG power in FNI infants ranged from 19% to 36% in frequencies from 10 to 48 Hz. The greatest percentage change (+36%) occurred during quiet sleep in the low gamma frequency range (25–36 Hz) in the frontal polar region. Robust effects were consistent, regardless of sex, singleton or twin status, gestational age at birth or birthweight.

In addition to EEG power, coherence affords another measure of brain activity and development. Coherence is a measure of the synchrony of cortical activity between two sites and reflects the phase-locking between two signals at any given frequency (12). In adults, EEG coherence is often viewed as a marker of functional connectivity between brain regions that underlies the processing of stimuli (13). From this perspective, increased coherence would seem desirable. However, Thatcher et al. (14) found there was an inverse relationship between resting state coherence and IQ. These authors suggest that lower coherence may be a marker for a greater capacity to process information. Consistent with this finding, Mundy et al. (15) found that 14-month-old infants with lower levels of short-distance frontal-central coherence at 6–9 Hz had better expression of joint attention at 18 months. Furthermore, high coherence has been linked to depression (16), ADHD (17) and schizophrenia (18).

There are a number of studies that have compared EEG functional connectivity in term and preterm infants. Duffy et al. (19) found reduced coherence in preterm infants between the frontal and occipital regions at 10 Hz and between the left central and temporal regions at 6–24 Hz. Our group reported that preterm infants have reduced frontal and parietal interhemispheric coherences, as well as reduced frontal polar to parietal-occipital intrahemispheric coherences at 1–12 Hz (20). However, at term age, preterm infants had increased interhemispheric coherence between occipital regions in the 24–50 Hz band, when compared with infants born at full term (20). Other studies comparing preterm and full-term infants found that differences in measures of EEG coherence were dependent on region, sleep state and frequency (21,22).

An alternative to comparisons of coherence between term and preterm infants is to assess how coherence changes with development. A recent study of preterm infants by Meijer and co-workers found that coherence declines with age from 26 to 38 weeks postmenstrual age (23). These authors speculated, similar to Thatcher (14), that lower coherence reflects greater functional differentiation of cortical areas.

Family Nurture Intervention was designed to improve emotional connection between mothers and infants with the overall goal of enhancing preterm development. In this study, we obtained sleep EEGs from FNI and SC preterm infants from 37 to 44 weeks PMA, and data were analysed to evaluate effects of the intervention on coherence. Based on a recent study showing that in preterm infants coherence decreases with age (23), we hypothesised that FNI would lead to decreases in coherence and would be consistent with our prior findings of increased frontal EEG power (11).

METHODS

Subjects and intervention procedures

Throughout the NICU stay nurture specialists engage the mother with her infant via scent-cloth exchange; individualised sessions facilitating maternal vocalisation, sustained eye contact, frequent and consistent skin-to-skin and clothed holding; and family-based support sessions (8). FNI activities begin as soon as possible after birth, while the infant is still confined to the incubator and continue until discharge. When the infant's health and development improve sufficiently to permit interaction outside the incubator, the mother continues to work with the nurture specialist on an individualised and regular basis (average 3.5 times per week) during calming sessions focused on emotional communication with her infant (9).

The FNI randomised-controlled trial was a parallel-group trial in the level IV NICU at the Morgan Stanley Children's Hospital of New York, Columbia University Medical Center, which compared standard NICU care (SC) with FNI. A complete description of the protocol was published previously (8). Briefly, 115 families with 150 preterm infants at 26–34 weeks postmenstrual age (PMA) were enrolled over a 42-month period from January 2009 through July 2012. Mothers in the FNI group met with nurture specialists who worked with them throughout the NICU stay to facilitate the intervention. FNI activities were initiated as soon as possible after birth and generally began with reciprocal scent-cloth exchanges. The mother placed a small cotton cloth in her bra and then placed another in the incubator at the head of her infant. She was encouraged to exchange her scent cloth with the infant's cloth at each visit to the NICU. As the infant became more stable, FNI mothers were encouraged to have contact with their infants, using firm and sustained touch, speaking in a soothing, emotional manner in their native language and making eye contact as often as possible. When the infant was medically able, FNI mothers were aided in skin-to-skin, and/or non-skin-to-skin holding with continuation of vocal soothing and eye contact. The mother was encouraged to engage in this mutual calming activity for at least one hour each session.

EEG acquisition

In this study, we report EEG results from 49 SC and 56 FNI near to term infants (37–44 weeks PMA). A prior report on

these same infants presented parental demographics, and maternal and infant clinical conditions that did not differ between groups (11). EEG used a multielectrode net (124 leads) and data acquisition system (EGI, Inc., Eugene, Oregon). EEG recordings were obtained between 11 am and 4 pm about 30 minutes after a normally scheduled feeding. Throughout the approximately one-hour-long recording sessions, research assistants observed the infants and assigned sleep-state codes (quiet sleep, active sleep) once each minute based on behavioural criteria (11). Quiet sleep is characterised by regular breathing, no eye movements and 'rag doll' tone. Active sleep is assigned when eye movements are observed, respiration is irregular, and body twitches are frequent.

EEG data acquisition was performed with a vertex reference. The signals from each lead were band-pass filtered from 0.1 to 400 Hz and then digitised with 16 bits per sample at the rate of 1000 samples per second. Data were notch-filtered to remove AC line noise at 60 Hz and its harmonics up to 500 Hz using a finite impulse response (FIR) filter. The signals were then re-referenced in software to an average reference montage providing 125 EEG channels. These filtered data were used to obtain measures of power (μV^2) and coherence at specific frequencies for each electrode. After the initial screening for artefact (see below), EEG coherence and power were computed using one-second fast Fourier transformations (FFTs) for each of the leads. Power was computed in 1-Hz band widths centred around each frequency. Thus, power at 2 Hz was the power from 1.5 to 2.5 Hz. Then, power was summed within ten contiguous bands. For simplicity of presentation, the upper frequency of each band was rounded down and the lower frequency of each band was rounded up. Thus, for example, power from 3.5 to 6.5 Hz was denoted as 4–6 Hz. The ten frequency bands used for this study were as follows: 0–3 Hz, 4–6 Hz, 7–9 Hz, 10–12 Hz, 12–14 Hz, 15–17 Hz, 18–20 Hz, 21–23 Hz, 24–36 Hz and 37–48 Hz. The one-second FFT results were averaged for each 30-second epoch throughout the recording session of each infant.

Multiple steps were taken to diminish inclusion of data that were contaminated by movement-related or other sources of artefact from noncortical electrical activity as follows. After placing the EEG net on the infant's head, electrodes were manipulated until impedances were below 50 k Ω . However, impedances can increase over the course of the study and cause excessively large voltages. The standard deviation of voltages was computed for every 30-second epoch for each of the leads, and data were excluded for individual leads within each epoch if their standard deviation exceeded 50 μV . In addition, data were excluded for entire epochs if more than 25% of the leads exceeded the standard deviation criterion during the epoch. Data for an entire study were excluded if more than 80% of the epochs failed to pass these criteria. Data from each lead were then re-referenced in each 30-second epoch to the average of the electrodes without artefact.

Prior to data analyses, we use two additional criteria for artefact rejection. We conducted regression analyses of log

power versus PMA at the time of the recording for each lead, frequency band and sleep state. Based on these regressions, outliers were defined as residuals whose studentised value (the ratio of the residual divided by the standard deviation of the residuals) exceeded 1.98 (i.e. $p \sim 0.05$ with $df \sim 300$).

Muscle artefact contributes to power at nearly all frequencies but, as a percentage of EEG power, most dramatically affects high-frequency power (24). Accordingly, if data from a lead were set to missing due to excessive power in the highest frequency band (37–48 Hz), the data for all frequency bands for that lead were set to missing.

Spectral coherence was computed using methods previously published by our group (20). Coherence is a measure of synchrony between two waveforms. It is thought that synchrony between EEG waveforms at two locations reflects similar brain function in the two locations (12). Coherence is a correlation measure and thus sensitive to artefacts common to both EEG leads. It is necessary to take particular care to minimise artefact because these can inflate coherence values. The common average reference has advantages over other references because it approximates the ideal 'reference-at-infinity' used in electromagnetic theoretical calculations of the potential from cerebral currents. An effective average reference requires a large number of electrodes and coverage of scalp surface. To improve accuracy at least three minutes of artefact-free data during a sleep state is used for measurement of coherence.

Statistical analyses

Coherence values were computed between all possible pairs of leads for ten frequency bands in two sleep states. In the first set of analyses, p -values from t -tests were used to exclude the subset of SC vs FNI tests among which 10% would be possible 'false discoveries', that is false discovery rate (FDR) of 0.10 (25). In addition, electrodes were grouped to define 12 regions as shown in Figure 1 (left and right frontal polar, left and right frontal, left and right temporal, left and right central, left and right parietal, left and right occipital). Then, analyses of covariance were used to determine significant effects of the intervention. Covariates included in these analyses were birthweight, twin status, sex and age at testing.

RESULTS

FNI effects on coherence: pairwise leads

Paired lead analyses revealed many significant (10% FDR threshold) effects of FNI on coherence although none of these was found above 21 Hz. Figure 2 shows the lead pairs (red lines) that had lower coherence in FNI than SC. These results were obtained in quiet sleep in the 10–12 Hz band. To evaluate these extensive differences, especially in frontal regions, we computed average coherences within and between all regions. We then applied analyses of covariance (covariates: birthweight, twin status, sex and age at testing) to determine differences in coherence between groups. The results obtained in quiet sleep and active sleep are shown in

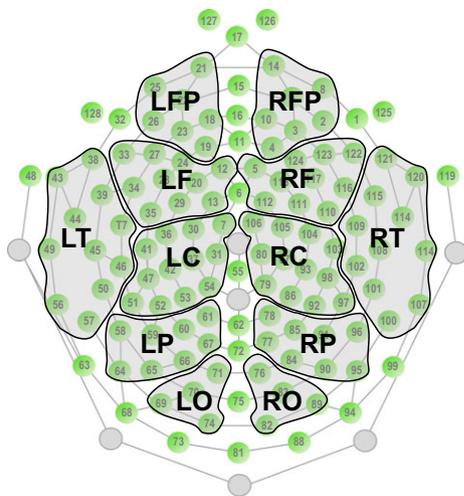


Figure 1 Shown are the individual leads used for EEG acquisition and the clusters of leads that defined 12 brain regions: LFP-left frontal polar, RFP-right frontal polar, LF-left frontal, RF-right frontal, LT-left temporal, RT-right temporal, LC-left central, RC-right central, LP-left parietal, RP-right parietal, LO-left occipital, RO-right occipital.

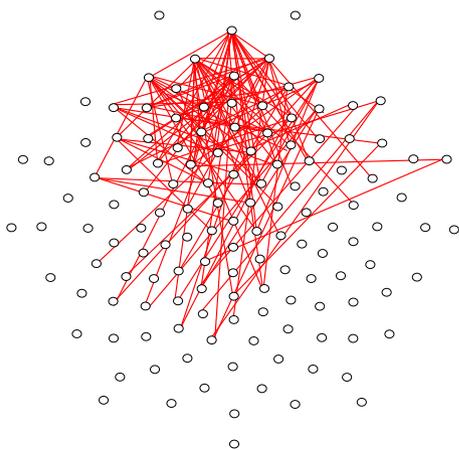


Figure 2 Red lines indicate electrode-to-electrode coherences at 10–12 Hz that were lower (FDR threshold = 10%) in Family Nurture Intervention (FNI) as compared to SC infants at term age. Data were obtained while infants were in quiet sleep.

Figures 3 and 4, respectively. There were significant reductions in EEG coherence within the left frontal polar region in frequencies from 4 to 18 Hz for the FNI group during quiet sleep, when compared to the SC group. Decreases in coherence within the FNI group were observed in the 0–3, 4–6, 7–9 and 10–12 Hz bands in the right frontal polar region. The most significant effects across both sleep states were reductions in coherence between the left and right frontal polar regions at 10–12 Hz (see red arrow in Fig. 3). In quiet sleep, there were also significant effects at longer distances (Fig. 3). These included 23 significant decreases between regions ($p < 0.01$ or $p < 0.001$). Fifteen of these significant differences were between hemispheres. As with

the data obtained during quiet sleep, analyses of active sleep data showed significant decreases in between-region coherences following FNI, but no robust effects of FNI on within-region coherences (Fig. 4).

Relationships between FNI effects on frontal polar coherence and power

In a prior report, we showed that at term age, infants in the FNI group had significant *increases* in EEG power in the frontal polar region (11). The most robust effect of the intervention was found during quiet sleep in the left frontal polar region in the 19–21 Hz frequency band. In this study of coherence, the most robust effect of FNI was a *decrease* in coherence between the left frontal polar and right frontal polar regions in the frequency band from 10 to 12 Hz, also during quiet sleep. To determine whether the effects of FNI on power and coherence were linked, we conducted analyses of covariance on both the FNI and the SC groups. The scatter plot of left frontal polar power (19–21 Hz) versus left to right frontal polar coherence (10–12 Hz) (Fig. 5) shows that power and coherence are negatively correlated in both groups; however, the correlations did not reach significance in either group (SC $p = 0.06$, FNI $p = 0.17$).

Finally, we conducted analyses of covariance to determine whether the FNI effects on power accounted for FNI effects on coherence and vice versa. Analyses revealed that the effect of FNI on power remained significant, even when controlling for coherence ($p = 0.003$), and the effect of FNI on coherence remained significant, even when controlling for power ($p = 0.024$).

Frontal polar coherence declines with age

Finally, we asked whether the age (PMA) of the infant at the time of EEG recording was correlated with the coherence variables that were affected by the intervention. The correlations between age and the *within* left frontal polar coherence (quiet sleep, 10–12 Hz) and the *between* left to right frontal polar coherence (quiet sleep, 10–12 Hz) were computed. The negative correlations between age and coherence were significant, in both *within region* (Fig. 6A) and *between regions* (Fig. 6B). These correlations between age and coherence were also significant in both the SC and FNI infants (within region: SC $r = -0.44$, $p < 0.002$, FNI $r = -0.40$, $p < .002$; between region: SC $r = -0.37$, $p = 0.009$, FNI $r = -0.30$, $p = 0.025$). The decreases in coherence with age were also significant in both SC and FNI for the three bands below 10 Hz (all p -values < 0.05 , data not shown).

DISCUSSION

Our prior results showed that FNI increased EEG power (10–48 Hz) in frontal polar regions (11). Here, we report FNI decreases coherence (1–18 Hz) in the same cortical region. We also found that 1–18 Hz coherence decreased from 37 to 44 weeks PMA within and between frontal polar areas in both SC and FNI infants. These developmental

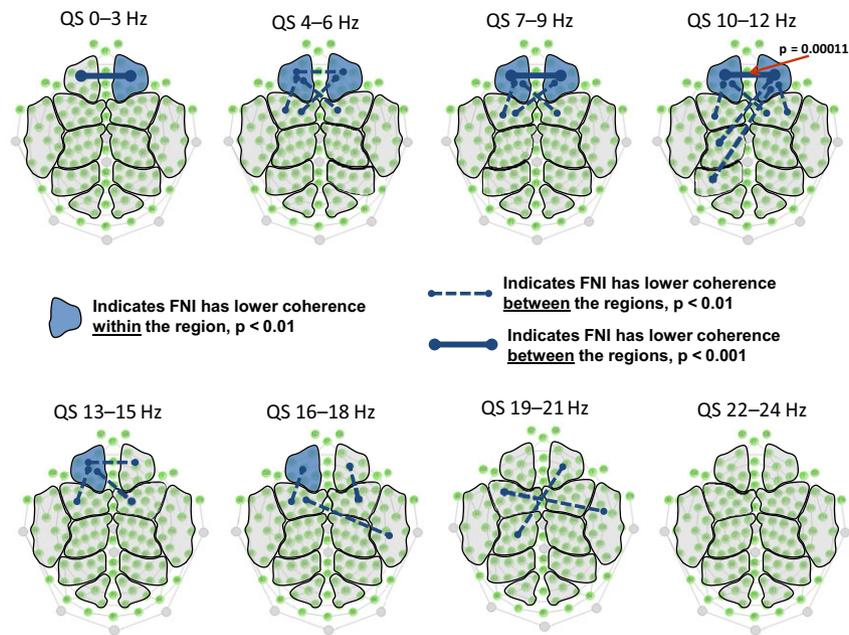


Figure 3 Shown are coherences that were significantly reduced in Family Nurture Intervention (FNI) versus SC infants. Data were obtained in quiet sleep (QS) at near to term age (37–44 weeks PMA). Each panel depicts results from a specific frequency band. Shaded areas indicate significant ($p < 0.01$) group differences within a region, dashed and solid lines indicate significant differences between regions ($p < 0.01$, $p < 0.001$, respectively).

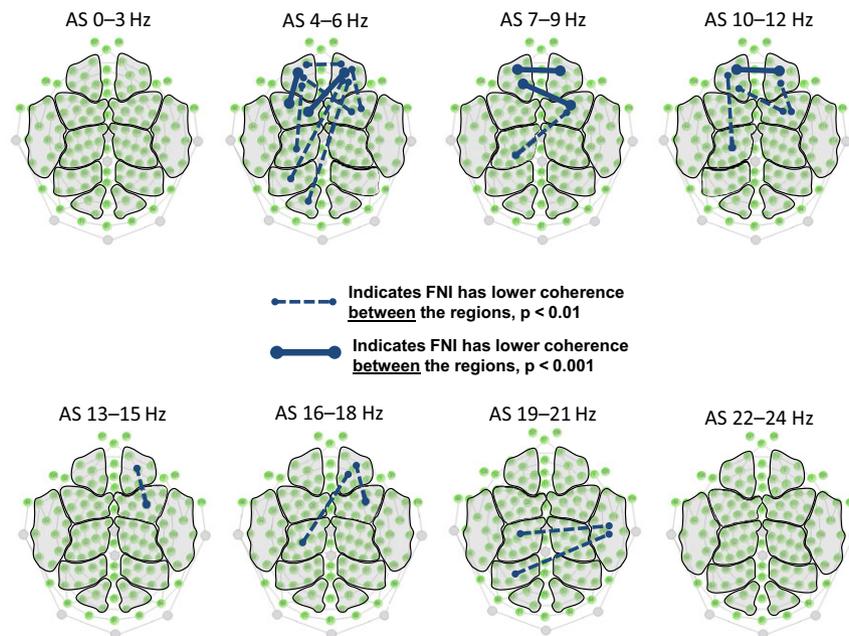


Figure 4 Shown are coherences that were significantly reduced in Family Nurture Intervention (FNI) versus SC infants. Data were obtained in active sleep (AS) at near to term age (37–44 weeks PMA). Each panel depicts results from a specific frequency band. Dashed and solid lines indicate significant differences between regions ($p < 0.01$, $p < 0.001$, respectively).

decreases in coherence are congruent with those of Meijer et al. (23) who also found systematic decreases in coherence with PMA. Our findings of group differences in

coherence (FNI < SC) coupled with a downward developmental trajectory of coherence with age suggest that FNI accelerates brain maturation, especially in the frontal

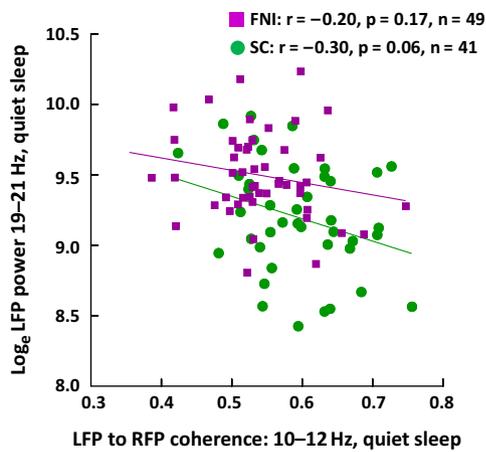


Figure 5 Scatter plot of left frontal polar power (19–21 Hz) versus left frontal to right frontal coherence (10–12 Hz). Data were obtained in quiet sleep at near to term age (37–44 weeks PMA). Green circles are data from SC infants, purple squares from FNI infants.

cortex. This is of particular relevance to the evaluation of neurobehavioral outcome of premature infants because the function of the frontal cortical region (26) is known to be impaired by premature birth (1–3).

EEG coherence reflects functional brain connectivity and has predictive value for defining neurodevelopmental outcome of infants (15). In a prior study comparing term infants with preterm infants at term age, we found that preterm infants had significantly reduced interhemispheric and intrahemispheric coherence below 12 Hz, but increased interhemispheric coherence between occipital regions at higher frequencies (24–50 Hz) (20). We concluded from these findings of regional differences in functional connectivity in very preterm infants that they may presage alterations in the structure of the developing cortex. We believe that the effects are due to reinstating critical mother–infant sensory, social and hormonal signals and that this signalling is mediated by mother–infant connectedness. The frontal cortex is highly responsive to

emotional stimuli in infants as well as in adults (27,28). The frontal cortical regions, where we found EEG changes suggestive of enhanced brain maturation, may be particularly affected mother–infant communication. Thus, intervention to enhance nurture may provide the emotional connectedness necessary to overcome the disruptions of mother/infant interactions due to preterm birth and to re-establish ongoing emotional communication interfered with by requisites for NICU care.

Analyses of data from the FNI trial show that power in the frontal polar region and coherence is negatively correlated, but that intervention effects on coherence at 4–6 Hz are not contingent on the significant effects of the intervention on power at higher frequencies. This difference in frequency dependency is consistent with separate effects of the intervention on power and coherence. Nonetheless, we considered the possibility that the lower coherence at 4–6 Hz in FNI infants might have been related to a nonsignificant lowering of power at 4–6 Hz, and thus might be dependent on changes in power via volume conduction. However, our prior study of EEG power (11) showed mean EEG power in the frontal polar region of FNI infants at term age was never lower than SC infants at any frequency or in either state. Moreover, we had previously reported that because of reduced volume conduction measures of EEG, coherence is more accurate in infants than in adults (29).

Our results suggest that the intervention may have two independent effects; increased power above 10 Hz (11), which we interpret as increased brain activity; and decreased coherence, which we interpret as a reflection of increased functional specialisation. During early development, active pruning and remodelling of circuitry may underlie regional specialisation of function that is shaped by experience. We found significant decreases in coherence with age within the left hemisphere of the frontal polar region and between the left and right frontal polar regions. The consistently lower values of coherence in FNI infants, as shown in Figure 6, imply that the intervention may promote maturation. Indeed, FNI outcomes at 18 months

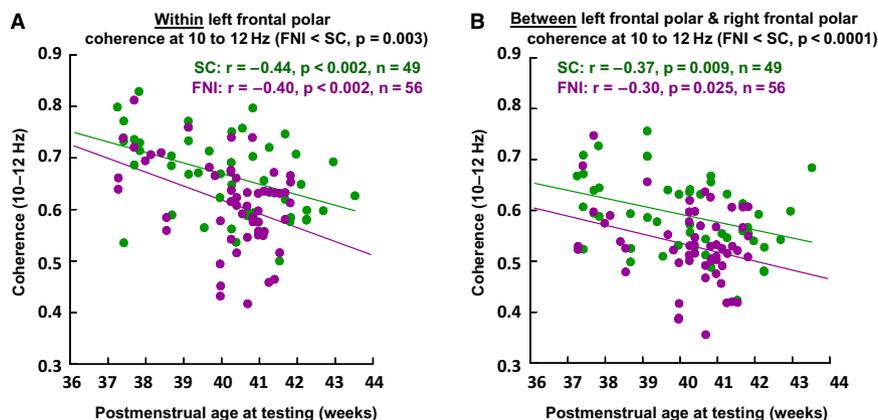


Figure 6 Scatter plots showing significant negative correlations between 10–12 Hz coherence and age for both SC and Family Nurture Intervention (FNI) infants. Panel A shows data within the left frontal polar region, panel B data between left and right frontal polar regions.

show improved neurodevelopment and greatly reduced risk for autism spectrum disorders (30). Thus, we hypothesise that FNI promotes brain circuit development in ways that guard against or prevent neurodevelopmental problems that are common in preterm infants.

CONCLUSIONS

At near to term age, analysis of the EEG in preterm infants shows treatment with FNI increases functional maturation, as reflected by decreases in low-frequency coherence within and between frontal cortical brain regions. These changes in coherence measures, together with high-frequency power increases reported previously, are found in regions known to be involved in attention, cognition and emotion regulation; domains that are negatively affected by premature birth and positively affected by social interaction. The fact that FNI has powerful effects on these brain regions supports the idea that interventions aimed at establishing mother–infant emotional connection during NICU hospitalisation may provide important neonatal care tools to overcome the adverse effects of preterm birth. Future analyses of data from this trial and its planned replication will test these hypotheses by evaluating correlations between early measures of brain activity, later measures of neurodevelopment and behaviour, and measures of mother–infant emotional connectedness.

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