Autonomic regulation of preterm infants is enhanced by Family Nurture Intervention

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RESEARCH ARTICLE

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Autonomic regulation of preterm infants is enhanced by Family Nurture Intervention

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Abstract

Preterm infants have maturational delays in several neurobehavioral systems. This study assesses the impact of the Family Nurture Intervention (FNI) in the neonatal intensive care unit (NICU) on the maturation of autonomic regulation of preterm infants. Preterm infants born at 26–34 weeks postmenstrual age (PMA) were assigned to groups receiving either standard care (SC) or SC plus FNI, using a randomized controlled trial design. At two collection time points, approximately 35 weeks and 41 weeks PMA, electrocardiograms (ECG) were monitored for approximately 1 hour during sleep. Heart rate and respiratory sinus arrhythmia (RSA) were quantified from the ECG. Across the two time points, the FNI group exhibited greater increases in RSA (Cohen's $d = 0.35$) and slope between RSA and heart rate, as a measure of vagal efficiency (Cohen's $d = 0.62$). These results document that FNI resulted in enhanced autonomic regulation consistent with greater maturation of cardiac function. These and previous findings strongly suggest that facilitating early nurturing interactions and emotional connection between preterm infants and their mothers is a practicable and effective means of optimizing postnatal development in preterm infants. Interpretation of these autonomic function results also enriches our understanding of the potential long-term beneficial outcomes of FNI by drawing upon polyvagal theory, which explains how autonomic state provides a neurophysiological platform for optimal co-regulation between infant and caregiver, and by drawing upon calming cycle theory, which provides a model for understanding how repeated mother/infant calming interactions positively condition autonomic state and reinforce approach, prosocial behaviors.

KEYWORDS
calming cycle theory, emotional connection, heart period, heart rate variability, polyvagal theory, respiratory sinus arrhythmia, vagal efficiency

1 | INTRODUCTION

Prematurity is found in 9%–12% of births in the US. Although advances in neonatal medicine have decreased mortality of preterm birth, surviving infants are vulnerable to multiple morbidities, including increased risk for medical problems (Barfield, 2018), attention deficits, cognitive and language delays, disturbed executive function, autism spectrum disorder (Agrawal, Rao, Bulsara, & Patole, 2018), anxiety and depression (Field, 2018), and cognitive impairment (Brydges et al., 2018). Among the contributors to these

outcomes are the effects of physical and emotional separation of infants and mothers during the neonatal intensive care unit (NICU) stay (Korja, Latva, & Lehtonen, 2012).

Considerable evidence suggests that after preterm birth neurodevelopmental interventions with infants, mothers, or both can have positive short-term effects (Benzies, Magill-Evans, Hayden, & Ballantyne, 2013; Chertok, McCrone, Parker, & Leslie, 2014; Moore, Bergman, Anderson, & Medley, 2016), although many studies lack design rigor (Ohlsson & Jacobs, 2013) and long-term prognosis for preterm infants, as noted above, is still poor. Nonetheless, basic science studies provide strong evidence that during early life, sensory stimulation embedded in mother–infant nurturing interactions is critical for shaping neurodevelopment (Tang, Reeb-Sutherland, Romeo, & McEwen, 2014).

This research, along with an intervention previously developed by Welch (1988), prompted the design of a novel in-hospital intervention, the Family Nurture Intervention (FNI), which aims to emotionally connect infants and mothers during the traumatic effects of early separation. The intervention utilized some techniques and procedures commonly practiced. However, FNI was singularly focused on a new measureable behavioral construct, autonomic emotional connection (Hane et al., 2018; Welch, 2016), as opposed to the conventional attachment and bonding constructs, which emphasize psychological connection (Chambers, 2017).

The initial randomized clinical trial (RCT), comparing FNI with standard care (SC) demonstrated feasibility and safety of the intervention (Welch et al., 2013), showed that FNI mothers exhibited increased maternal sensitivity during normal caregiving activities when their infants were approximately 36 weeks postmenstrual age (PMA) (Hane et al., 2015), and decreased symptoms of anxiety and depression when their infants were 4 months corrected age (Welch et al., 2016). At ~41 weeks PMA, FNI infants had robustly increased high-frequency electroencephalogram (EEG) power (Welch et al., 2014), altered EEG-based functional connectivity (Myers et al., 2015), and advanced maturation (Welch et al., 2017). At 18 months corrected age, FNI infants had improved scores on the Bayley-III, fewer attention problems on the Child Behavioral Check List, and decreased risk for socio-emotional problems as assessed by the Modified Checklist for Autism in Toddlers-Revised (Welch et al., 2015).

In the current study, maturational changes in autonomic regulation were evaluated during the period while the infants were receiving FNI or SC in the NICU or shortly thereafter. Polyvagal theory forms the theoretical bridge linking the attribute of emotional connection in FNI as a facilitator of more optimal maturation of autonomic regulation and enhanced co-regulation (Porges, 1995, 2007, 2009, 2015; Porges & Furman, 2011). Polyvagal theory highlights the ontogenetic transitions in the neural pathways that regulate autonomic state and provide an understanding of how autonomic state provides a neurophysiological platform for the optimal co-regulation between infant and caregiver. The theory articulates the mechanisms through which the maturation and myelination of vagal pathways are involved in the regulation of

visceral state (e.g., heart rate) and how vagal pathways are bidirectionally linked with the brainstem areas controlling many of the attributes of social engagement (e.g., facial expression, gaze, and vocalizations) through well-defined visceral efferent pathways in several cranial nerves.

Informed by the literature documenting the maturation of autonomic regulation during gestation (Porges & Furman, 2011), it is possible to interpret maturational shifts observed during the intervention with the same metrics monitored in other studies with preterm infants (DiPietro & Porges, 1991; Feldman & Eidelman, 2003; Porges, 1992; Portales et al., 1997; Suess et al., 2000) and healthy full-term newborns (Porges, Doussard-Roosevelt, Stifter, McClenny, & Riniolo, 1999). The above cited studies have applied a validated method of quantifying a component of heart rate variability known as respiratory sinus arrhythmia (RSA) to index cardiac vagal tone (Lewis, Furman, McCool, & Porges, 2012; Porges, 1985b). RSA is observed as a rhythmic increase and decrease in heart rate that occurs at the frequency of spontaneous breathing. RSA is conveyed through myelinated vagal pathways originating in the brainstem area known as nucleus ambiguus. This respiratory rhythm was identified more than a century ago in 1910 by Hering (1910), who noted that the inhibitory electrical discharge through the vagus to the heart's pacemaker (i.e., sino-atrial node) had a respiratory rhythm. Thus, the quantification of RSA has become a contemporary method to index cardiac vagal tone.

In this study, we use two measures to evaluate the vagal maturation and regulation of the heart. Based on the literature (see above), RSA was monitored as an index of cardiac vagal tone to evaluate maturation, since RSA exhibits a developmental curve similar to histological reports of myelination of the vagus (see Porges & Furman, 2011). In addition to RSA, we measured the slope between the dynamic and synchronous shifts in RSA and heart period, which provides a measure of regulation of heart rate by vagal pathways. This we refer to as "vagal efficiency," a concept first introduced as an extension of polyvagal theory in 1999 (Porges et al., 1999). According to polyvagal theory (Porges, 1995; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996), the vagal brake is conceptualized as an adaptive neural physiological mechanism that fosters engagement and disengagement with the environment. The efficiency of the vagal brake can be assessed by calculating the relationship between synchronous measures of the amplitude of RSA and heart period quantified in sequential 10 s epochs during each sleep state. As illustrated in Figure 1, vagal efficiency increases as the slope between heart period and RSA becomes steeper. In the left panel of Figure 1, for each log unit change in RSA, there is a change in heart period of 9 msec. In the right panel of Figure 1, for each log unit change in RSA there is a change in heart period of 19 msec. These plots illustrate how changes in cardiac vagal tone (measured by RSA) will differentially influence heart period.

Since this novel measure has been documented to exhibit sleep-state differences in full term newborns, quantification in this study provided an opportunity to evaluate the influence of FNI, which is aimed at establishment of emotional connection, on the
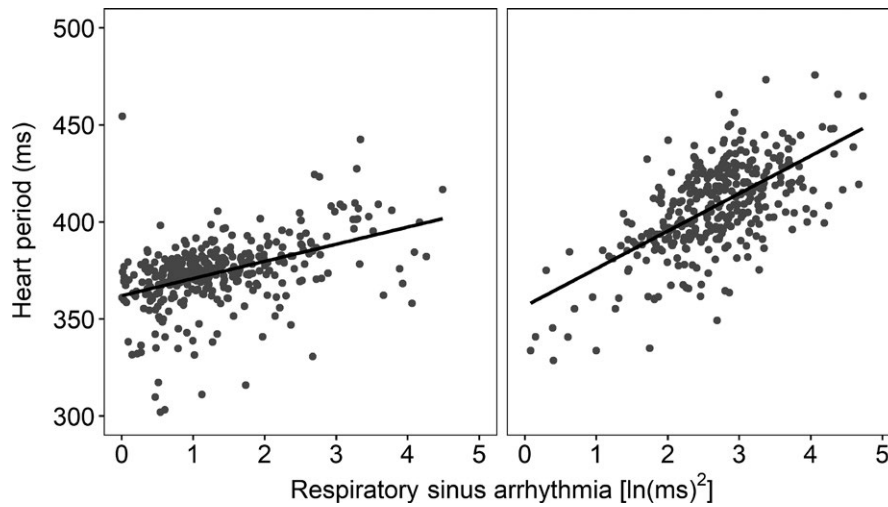
FIGURE 1 Example of vagal efficiency defined by the slope of synchronous within state 10 s measures of respiratory sinus arrhythmia (RSA) and heart period. Though both infants have a similar range of vagal tone values (measured by RSA), the infant on the left has not as low-vagal efficiency (slope = 9.16), suggesting that a vagal brake has a weak effect on heart period. The infant on the right has high-vagal efficiency (slope = 19.36), suggesting that changes in cardiac vagal tone have a stronger effect on dynamic changes in heart period. As would be expected from a more efficient vagal brake, the infant with higher-vagal efficiency (right panel) also has a longer-mean heart period

maturational shift of this variable and its ability to distinguish between sleep states.

2 | METHOD

2.1 | Intervention procedures

Shortly after birth, after obtaining permission from the attending physician (average 7 days), a research assistant approached the mother (and father if present) to explain the study and obtain written consent. The consented families were assigned to either FNI or SC using a computer-generated block randomization. Twin randomization was conducted at the level of the family. Mothers were randomized and twins were jointly assigned with their mother to a single group. After consent, mothers assigned to the FNI group met with Nurture Specialists, who worked with the mother, infant, and family throughout the study to facilitate all aspects of the intervention. Mothers and infants assigned to the SC condition received the care that is standard for infants admitted to the NICU participating in this study.

Nurture Specialists initiated the first FNI activities approximately 1 week after birth while the infant was still in the incubator. The Nurture Specialists were nurses trained by the staff at the Nurture Science Program in all aspects of the intervention procedures. The first intervention procedure involved engaging mothers and their infants in "calming sessions." This involved mothers' communicating directly and emotionally with their infants for a prolonged period, usually 1 hour or more, until the infant and mother were noticeably calmer. FNI mothers were facilitated in making contact with their infants through the ports of the incubator, using firm and sustained touch. Each mother was provided two small cotton cloths, one to wear in her bra and the other to place under the head of her infant, which they were encouraged to exchange daily. The mothers were led by the Nurture Specialist to speak

directly to their infants in an emotional manner, including expression of their upset feelings about the early birth, their infant's fragile condition, and about the hardships posed to the pair by NICU care. They were asked to speak in their native language, the emotional language spoken to them by their own mothers and family, while establishing eye contact. On average, the FNI mothers engaged in these activities for 6 hr/week (Welch et al., 2013).

When the infants were sufficiently stable to leave the incubator, FNI mothers were encouraged to engage in calming sessions, including skin-to-skin or non-skin-to-skin holding, vocal soothing, emotional expression, and eye-to-eye contact. During these calming sessions, Nurture Specialists assisted mothers in holding their infants safely and securely in an upright position while the mother was comfortably seated in a reclining chair. Once initiated, mothers engaged in these mutual calming activities for one hour, or as long as possible during each calming session. The mothers continued to work with Nurture Specialists on an individualized, regular basis (i.e., an average of 3.5 times/week for an average of 6 weeks) during calming sessions focused on emotional communication with her infant.

When family members were available to meet, Nurture Specialists engaged them in sessions that focus on discussions of the importance of the calming session activities. These family sessions, which usually occurred near the end of the NICU stay, were designed to help families understand the unique emotional needs of a preterm infant and to encourage the family units to continue supporting the mother and infant in a regular calming cycle routine after discharge from the hospital.

Given the heterogeneity of the preterm infants recruited in this study, there were variations in the duration between birth and the initiation of FNI (median = 7.0 days, minimum–maximum = 1–14 days) and between the initiation of FNI and the first assessment of autonomic regulation (median, 13 days; range 4 to 35 days).

2.2 | Subjects

The experimental design was a RCT comparing SC and FNI within the NICU. The study was conducted in the level IV NICU at the Morgan Stanley Children's Hospital of New York, Columbia University Medical Center. A complete description of the protocol was published previously (Welch et al., 2012). Briefly, 115 families with 150 preterm infants at 26–34 weeks PMA were enrolled over a 42-month period from January 2009 through July 2012.

Maturational changes in heart rate patterns were measured at two time points. The first or "early" measure occurred between 34 and 37 weeks PMA (~35 weeks) and the second, "near-to-term," between 37 and 44 weeks PMA (~41 weeks PMA). Due to the focus of this paper on the differential influences of SC and FNI on maturation of the autonomic nervous system, only infants with quantifiable electrocardiogram (ECG) data during both active and quiet sleep states within both sessions were analyzed. In this study, heart rate data are presented from 59 infants who fit the following criteria: (1) sufficient ECG data to obtain reliable measures (i.e., at least four 30-s epochs) during each sleep state within each session and (2) had both early and near-to-term assessments with an interval of 2 weeks or more.

Of the original 150 subjects enrolled, 59 provided sufficient ECG data to calculate the variables evaluated in the analyses. To determine if there were differences between subjects included and not included, and if so whether such differences were similar in the two treatment groups, two-way ANOVAs with treatment group (SC vs. FNI) and study inclusion (included vs. not included) were tested for several key infant and demographic variables. These analyses also determined if there were significant interactions between treatment and inclusion groups. Analyses were conducted for GA at birth, birthweight, delivery mode (spontaneous vs. caesarian section), length of stay in the NICU, sex, mother and father ages, and mothers' education. The analyses revealed a small, but significant difference in GA at birth ($p = 0.009$) with the included subjects being approximately 0.5 weeks older. This difference was paralleled by a greater birthweight ($p = 0.035$) and shorter length of stay in the NICU by the inclusion group ($p = 0.014$). However, these differences were similar for both SC and FNI. There were no significant differences in mother or father ages or education, as indexed by the maternal education. Analysis of mother's age revealed a significant intervention group by inclusion group interaction ($p = 0.045$), with FNI mothers being 3.6 years older in the not included group but 0.9 years younger in the included group. Overall, the analyses support the conclusion that the group differences observed in the autonomic measures were not related to a systematic bias in characteristics of infants in the inclusion and treatment groups. Inclusion and exclusion samples did not differ on timing of assessments or on key outcome variables (see Table S1).

Of the 59 infants in this study, 28 were in the SC group and 31 in the FNI group. Table 1 provides information on birthweight, gestational age birth, age at the early test session, age at the near-to-term session, and interval between test sessions. Note that the FNI group was significantly older during the second session, which contributed to the FNI group having greater durations between testing sessions. Although not significantly different, the lowest birthweight infants were randomly assigned to the FNI group. The inclusion of twins in this study contributed to this potential bias and was not observed in PMA. Thus, birthweight and the time between test sessions were used as covariates in the analyses of variance models. Groups did not differ by infant sex (SC males = 39.39%; FNI males = 45.16%; $\chi^2 = 0.04$, $df = 1$, $p = 0.85$).

2.3 | ECG acquisition

ECG recordings were made in conjunction with an EEG study (Welch et al., 2014). Data were collected between 11 a.m. and 4 p.m. within 30 min after a normally scheduled feeding. The ECG signal was acquired at 1 kHz via electrodes placed on the infant's chest with a Biopac MP 150 physiological acquisition system (Biopac Systems, Inc., Santa Barbara, CA). ECG data were collected for approximately 1 hour, while research assistants coded sleep state (i.e., quiet, active, indeterminate, awake, and crying) during each sequential minute. Sleep state was coded using behavioral criteria previously demonstrated to be appropriate for preterm infants (Stefanski et al., 1984).

TABLE 1 Infant characteristics

Variable	Group	n	Mean	SD	Min	Max	t	df	p
Birthweight (grams)	Standard care	28	1,605.18	368.31	940.00	2,605.00	1.18	57	0.244
	FNI	31	1,493.94	357.54	792.00	2,380.00			
Gestational Age (weeks)	Standard care	28	31.62	1.86	26.43	34.71	0.92	57	0.364
	FNI	31	31.16	1.99	27.14	34.86			
Age at "early" session (weeks)	Standard care	28	34.85	0.73	33.57	36.57	0.79	57	0.432
	FNI	31	34.70	0.74	33.57	36.43			
Age at "near-to-term" session (weeks)	Standard care	28	40.01	1.58	37.43	42.29	−2.55	57	0.013
	FNI	31	41.00	1.39	36.71	44.43			
Interval between sessions (weeks)	Standard care	28	5.16	1.69	2.14	7.14	−2.71	57	0.009
	FNI	31	6.30	1.53	2.00	10.00			

FNI: Family Nurture Intervention; SD: standard deviation.

Due to limitations in representations of sleep states during the 1-hour data monitoring session, analyses were conducted only on data collected during quiet and active (REM) sleep. Quiet sleep was assigned when the infant had regular breathing, no eye movements, and low muscle tone. Active sleep was assigned when eye movements were observed, respiration was irregular, and body twitches were frequent.

The digitized data were processed with software that detected the inflection point of the R-wave and the interval (i.e., heart period) between sequential R-waves to the nearest ms. The sequential heart periods were visually inspected and edited offline with a modified version of CardioEdit+ software (Brain-Body Center for Psychophysiology and Bioengineering, Department of Psychiatry, University of North Carolina at Chapel Hill). Editing consisted of two sequential methods. The first method focused on the time series of heart periods and identified atypical heart periods due to missed or faulty detections of R-waves. In most cases, atypical beats could be edited by adding adjacent periods together and then dividing, or dividing an atypical long interval due to a missed R-wave detection. However, anomalies in ECG patterns were occasionally observed when very short heart periods were not followed by compensatory pauses. Anomalies, such as an isolated short beat, cannot be edited by integer arithmetic (e.g., adding and dividing adjacent intervals). Nor can the isolated short beat be edited by removing it from the time series of heart periods, since removal would disrupt the continuity of the data and violate a necessary assumption for the times series analyses used to quantify the oscillations in heart rate that define RSA. To deal with these cases, a second editing routine was developed that indexed data by time and not sequential beats. This strategy required that the edited output of heart periods from the initial editing phase be time sampled. In the second phase of editing, the heart period time series was time sampled at 5 Hz and anomalous values of the time-sampled heart periods were identified as deviations outside the range 75% to 137.5% of the preceding second of data. When an outlier was identified, a linear interpolation connected the brief segments of valid heart periods. Consistent with reports that heart period exhibits a stronger linear relation with autonomic control than heart rate (Berntson, Cacioppo, & Quigley, 1995; Quigley & Berntson, 1996), all cardiac variables evaluated in this study were quantified from heart period time series.

2.4 | Data quantification

After the data were edited, a modified version of CardioBatch+ calculated heart period, the amplitude of RSA, and RSA frequency (see computation methods below) in sequential epochs that were synchronized with the sleep-state codes. CardioBatch+ calculates the amplitude of RSA with the Porges–Bohrer method (Lewis et al., 2012; Porges, 1985a), which employs a time-frequency method to extract from the heart period time series a frequency band-limited component representing RSA. This strategy maximized representation of physiological variables during short epochs (30 s) of sleep, when the infant's sleep pattern may be unstable and represented by transitory state shifts. In addition, regression analyses between RSA and heart period based on extremely short epochs (10 s) enabled the evaluation of the efficiency of vagal regulation (i.e., ms change in heart period per unit change in RSA, Porges et al., 1999).

The Porges–Bohrer method involves the following sequential steps (Lewis et al., 2012; Porges, 1985a; Porges & Bohrer, 1990). First, when applied to newborn infants, heart period values are measured to the nearest ms and resampled into equal time intervals every 200 ms. Second, a detrending algorithm removes from the heart period times series the variance associated with complex aperiodic baseline shifts and oscillations slower than RSA. The detrending algorithm applies a moving polynomial filter (3rd order, 21 point, 4.2 s duration) to remove aperiodic baselines and slow oscillations. Third, the residual output from the moving polynomial is band-passed, and the heart period variance in the frequency band associated with spontaneous breathing in the newborn (i.e., 0.3–1.3 Hz) is quantified. Fourth, to reduce distribution skewness associated with variance estimates, the band-passed variance is transformed with a natural logarithm and reported in units of ln $(ms)^2$ as RSA. In addition, spectral analysis was performed on the detrended data (i.e., time sampled every 200 ms and detrended with a third order, 21-point moving polynomial) to determine the frequency (i.e., frequency of peak of the spectrum) of RSA.

Consistent with other studies in which similar methods have been used (i.e., MXedit, CardioBatch, and CardioBatch+) with neonates (Porges, 1992; Porges et al., 1999; Portales et al., 1997; Suess et al., 2000), epoch durations of 30 s were used to quantify RSA and heart period. An average of the within sleep state epoch values were used in the statistical analyses for heart period, RSA, and the frequency of RSA.

Since RSA provides a validated metric of cardiac vagal efferent tone through pathways originating in nucleus ambiguus (Lewis et al., 2012), this study evaluated how RSA was related to heart period and how this relationship changed with maturation and the interventions administered within the NICU (i.e., contrasting FNI with SC). By calculating the slope of the regression between transitory levels of heart period and RSA over very short epochs (10 s), an index of the efficiency of vagal regulation (i.e., vagal efficiency) of heart rate was generated. Functionally, this measure quantified the impact of vagal efferent pathways on heart rate.

2.5 | Metrics

The following variables were generated for each infant within each sleep state and test session:

1. Heart Period: The average time between sequential heart periods in ms. Statistically, this measure is the reciprocal of heart rate (i.e., as heart period expands in duration, heart rate slows), but has better distributional features for parametric analyses. Heart period increases with age and maturation due to increases in parasympathetic to sympathetic balance in autonomic regulation.

2. Respiratory Sinus Arrhythmia (RSA): The average of the natural log-transformed epoch-based measures of the amplitude of RSA. RSA, an indirect measure of parasympathetic regulation of heart rate (heart period), increases with age and maturation.

3. RSA Frequency (RSAf): The average of epoch-based measures of peak frequency of RSA derived from spectral analyses conducted on the detrended time sampled (i.e., 5 Hz) heart period using the Porges–Bohrer moving polynomial filter. The peak of the detrended spectrum provides an estimate of respiration rate. In previous research, this method has been used as an estimate of respiration rate and correlations with chest movement approach 1.0 (Denver, Reed, & Porges, 2007). Respiratory rate slows with maturation and age.

4. RSA/Heart Period coupling (vagal efficiency): RSA and heart period were calculated in sequential 10 s epochs and clustered within each sleep state. The slope from regression analyses between the epoch-based heart period and RSA values within each sleep state during each session defined RSA-heart period coupling as an index of the efficiency of vagal regulation of heart rate (Porges et al., 1999). This measure of autonomic regulation would be expected to increase with age and maturation.

2.6 | Design and analyses

As noted above, data were collected during two sessions: The first or "early" session was at ~35 weeks PMA and the second or "near-to-term" session was at ~41 weeks PMA. As described in Table 1, at the start of the study infant clinical conditions did not differ between groups. Within each of the two test sessions, after the ECG files were transformed into a heart period time series and edited, the data were segmented into periods of active and quiet sleep. The heart period time series were processed to quantify epoch-based indices of heart period, RSA, RSAf (i.e., respiration rate), and the efficiency of vagal regulation of heart rate (slope of the linear regression of RSA on heart period).

Since there were no differences in physiological measures as a function of sex, all analyses reported are collapsed across sex. To deal with unequal variances in a repeated measures design, the data were analyzed with linear fixed effects models (Verbeke & Molenberghs, 2009) and were implemented using the restricted maximum likelihood estimator in the SPSS Mixed function procedure. The effects of session (e.g., ~35 weeks PMA and ~41 weeks PMA), sleep state (active and quiet), and treatment group (SC and FNI) were assessed for main effects and interactions. Sleep state and session were treated as repeated measures. Birthweight and duration of the interval between test sessions were included as covariates in all models. The covariance structure was estimated using heterogenous compound symmetry, which allows for the heterogenous variable variances that may arise with repeated measures (Wolfinger, 1996). Significant interactions were probed using pairwise comparisons derived from the marginal means. Effect sizes for categorical predictors were measured with Cohen's d (Cohen, 1988).

3 | RESULTS

3.1 | Respiratory sinus arrhythmia

Although the duration between test sessions was a significant covariate $F (1, 56.5) = 6.8$, $p = 0.012$, it did not interact with any factor or interaction. RSA exhibited a significant Group by Session interaction, $F (1, 161.95) = 4.72$, $p = 0.031$. As illustrated in Figure 2, the increase in RSA from ~35 weeks PMA to ~41 weeks PMA was significantly greater in the FNI group (Cohen's $d = 0.35$). In addition, there was a significant session effect, $F (1, 161.95) = 153.71$, $p < 0.001$ (Cohen's $d = 1.07$). RSA increased from 1.53 ln (ms^2, $SE = 0.09$) to 2.45 ln (ms^2, SE = 0.10).

3.2 | RSA frequency

For each continuous segment of data within each sleep state, spectral analyses were conducted to identify the peak frequency within the frequency band in which RSA was defined (i.e., 0.3–1.3 Hz). The average across segments provided the index of RSAf. Analyses indicated a significant difference between quiet sleep (0.67 Hz or approximately 40 cycles/minute) and active sleep (0.63 Hz or approximately 38 cycles/minute), $F (1, 164.62) = 9.47$, $p = 0.002$ (Cohen's $d = 0.41$). There were no significant effects of FNI group membership or its interaction with sleep state and session (all $p > 0.05$).

3.3 | Heart period

As the preterm infants matured, there was a significant slowing of heart rate reflected in an increase in heart period from ~35 weeks PMA to ~41 weeks PMA, $F (1, 134.7) = 112.54$, $p < 0.001$. The average heart period, combined across groups, increased from 384.92 ms ($SE = 2.87$; 155.9 bpm) during the early session to 412.41 ms ($SE = 3.63$; 145.5 bpm) during the near-to-term session (Cohen's $d = 1.01$).

Across sessions and groups, there was a significant slowing of heart rate reflected in longer heart periods during quiet sleep relative to active sleep, $F (1, 147.16) = 10.88$, $p = 0.001$. During quiet sleep, the average heart period was 402.91 ms ($SE = 3.59$; 148.9 bpm) compared to 394.4 ms ($SE = 2.91$; 152.1 bpm) during active sleep (Cohen's $d = 0.37$). There were no significant effects of FNI group membership or its interaction with sleep state and session (all $p > 0.05$).

3.4 | Vagal efficiency

The slope of the regression between changes in heart period and RSA significantly increased as the infants matured from ~35 weeks PMA to ~41 weeks PMA $F (1, 147.43) = 50.61$, $p < 0.001$. The slope increased from 9.77 ($SE = 0.70$) to 16.33 ($SE = 0.99$; Cohen's $d = 0.95$). At ~35 weeks PMA, this indicated that a change of 1 ln unit in RSA resulted in a change in heart period of less than 10 ms, while at approximately term age a change of 1 ln unit in RSA resulted in a change of more than 16 ms.
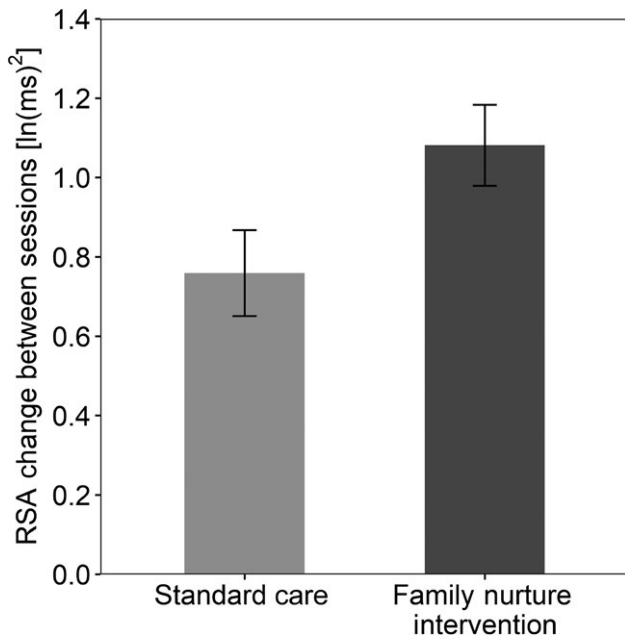
FIGURE 2 As the infants approached term, increases in respiratory sinus arrhythmia were significantly greater in infants receiving Family Nurture Intervention compared to the standard care group ($p = 0.031$; Cohen's $d = 0.38$; error bars represent standard error)

FIGURE 3 As the infants approached term, increases in vagal efficiency were significantly greater during active sleep ($p = 0.019$; Cohen's $d = 0.40$; error bars represent standard error)

Across test sessions, sleep state influenced vagal efficiency. The slope was greater during active sleep (15.50, $SE = 0.96$) than during quiet sleep (10.59, $SE = 0.74$), $F_{(1, 149.23)} = 28.83$, $p < 0.001$ (Cohen's $d = 0.80$) (Figure 3). Moreover, as illustrated in Figure 4, there was a significant Session by Sleep-State interaction, $F_{(1, 150.29)} = 5.66$, $p = 0.019$. Although greater slopes were observed during active sleep during both sessions, there was a greater maturational increase in slope during active sleep relative to quiet sleep (Cohen's $d = 0.40$).

Although both SC and FNI infants exhibited a maturational increase in the slope between RSA and heart period (i.e., vagal efficiency), the groups differed in these age-related changes. As illustrated in Figure 4 the FNI group experienced a greater rate of increase in vagal efficiency. This was supported by a significant Session by Group interaction, $F_{(1, 147.43)} = 8.02$, $p = 0.005$. Specifically, although at the ~35-week time point, the FNI group had a significantly lower slope, by term age the FNI group had crossed over the trajectory of the SC group (Cohen's $d = 0.62$).

4 | DISCUSSION

FNI was designed to help reestablish the emotional connection (Hane et al., 2018) between mothers and their infants that was disrupted by the preterm delivery and the experiences of mother and infant within the NICU. Findings thus far have shown that FNI led to greater maternal sensitivity during routine caregiving behavioral interactions (Hane et al., 2015), altered in brain activity and functional
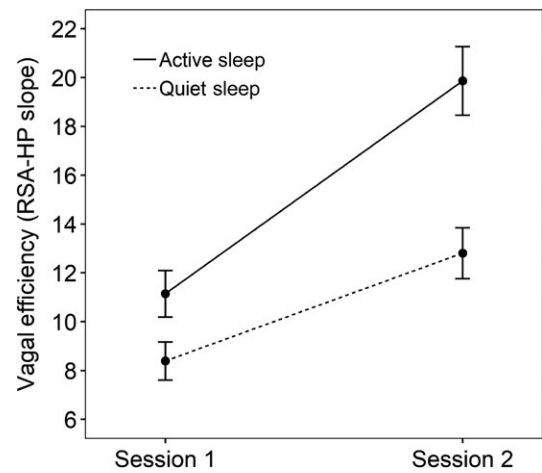
connectivity consistent with accelerated brain maturation, particularly in frontal regions (Myers et al., 2015; Welch et al., 2017), lowered symptoms of maternal depression post discharge (Welch et al., 2016), and improved neurobehavioral outcomes to 18 months of age (Welch et al., 2015). Given the emphasis of the intervention on dyadic emotional connection and the linkage between autonomic activity, emotion regulation, and social engagement (Porges, 2007, 2009), we hypothesized that with improved emotional connection FNI infants would exhibit signs of a more mature vagal regulation system very early in life (Welch & Ludwig, 2017a, 2017b). It is interesting to note, for instance, that infants later diagnosed with autism demonstrated slower increase of RSA between age 1 and age 6, as compared with non-autistic infants (Sheinkopf et al., 2019). Future studies will evaluate the covariation of these early indices of autonomic maturation with the concurrent measures of EEG previously reported (see above citations) and behavioral and autonomic assessments obtained from the subjects after they were discharged from the NICU.

Collection of ECG signals during the EEG recording sessions at approximately 35 weeks PMA and again at approximately 41 weeks allowed us to quantify RSA as a marker of these proposed effects. Consistent with our hypothesis, results from the current analyses show that the increased RSA, a marker of cardiac vagal tone and autonomic regulation, occurring between the early to the near-to-term age time points were significantly greater in the FNI group. In addition, the slope between RSA and heart period, an index of vagal regulation efficiency, was significantly steeper in the intervention group. We interpret both of these findings as evidence of accelerated maturation of autonomic control in FNI infants. Heart period and RSAf measures, reflecting less well-defined vagal influence, were not sensitive to intervention assignment.

The mechanisms through which FNI accelerated the maturation of vagal regulation are as yet unclear. However, we have proposed that Pavlovian conditioning of autonomic states may underlie these effects. According to calming cycle theory, the calming routine, which involves communication of affect during comfort touch, vocal soothing, emotional expression, eye-to-eye contact, and skin-to-skin (or
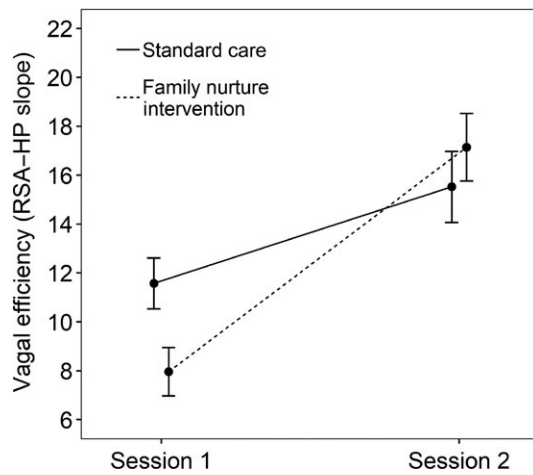
FIGURE 4 As the infants approached term, increases in vagal efficiency were significantly greater in infants receiving Family Nurture Intervention compared to the standard care group ($p = 0.005$; Cohen's $d = 0.62$; error bars represent standard error)

clothed) holding, facilitated emotional connection between mother and infant, which resulted in approach behaviors, and co-conditioning of calming reflexes in both mother and infant (Welch, 2016; Welch & Ludwig, 2017a, 2017b). In other words, the mother/infant calming sessions, which were facilitated by Nurture Specialists in the NICU, provided opportunities to pair positive approach behaviors of both mother and infant with a high-cardiac vagal tone, calmness, and regulated autonomic state. This repeated pairing over time results in a conditioning of an adaptive cardiac calming reflex upon contact.

The calming cycle theory is consistent with the polyvagal theory, which suggests that repetition of the reciprocal behaviors function as a neural exercise of the mother's and infant's Social Engagement Systems (Porges, 2007, 2009; Porges & Furman, 2011). By exercising the Social Engagement System, the cranial nerves (i.e., V, VII, IX, X, XI) involved in the regulation of the striated muscles of the face and head (through special visceral efferent pathways), and the heart (through the myelinated vagal pathways originating in the nucleus ambiguus) are recruited for social engagement and state regulation. Thus, repeated engagement of these systems not only conditions an adaptive cardiac calming reflex upon contact, but also enhances resilience by promoting maturation of these systems during early development.

It is reasonable to ask whether more rapid development of autonomic control is of benefit to the infant. Currently, the answer to this question must rely on correlative evidence. First, the more rapidly increased RSA and vagal efficiency seen in FNI infants were similar to values for RSA and vagal efficiency measured in full term infants in a prior study (Porges et al., 1999). This suggests that SC preterm infants lag in their autonomic development and that FNI promoted normalization in maturation in these systems. Second, as noted above, FNI resulted in positive outcomes across multiple dimensions when the infants reached 18 months of age. Thus, the acceleration in autonomic regulation early in life presaged positive outcomes a year and a half later. Again, these data support the conclusion that

acceleration of neural regulation of autonomic function (RSA, vagal efficiency) and central nervous activity (EEG power and coherence) were likely early markers of positive effects of the intervention. Analyses examining whether these early physiologic markers are predictive (i.e., correlated) with long-term outcomes are currently being evaluated.

Although the developmental trajectories of RSA and vagal efficiency were steeper in FNI infants, values for vagal efficiency were actually lower in FNI infants at the early time point. It is interesting that for some brain regions we noted a similar effect on EEG power. That is, in some brain regions EEG power was lower in FNI infants at the early time point, but increased more rapidly to term age (Welch et al., 2014, 2017). It is possible that the random assignment procedure used in the RCT actually created groups that had features that were not equivalent at the time of enrollment. Alternatively, since the early assessment time point at ~35 weeks PMA occurred on average about 5 weeks after the start of the intervention, it is possible that very early in the NICU stay the FNI slowed initial rates of development before subsequently promoting acceleration. Results from an ongoing multisite replication trial of FNI (Clinicaltrials.gov: NCT01439269) will help distinguish these alternatives.

The results indicate that RSA is selectively affected by FNI, while heart rate and respiratory rate (RSAf) were not. The lack of an effect on RSAf, suggests that the intervention's effect on RSA (i.e., cardiac vagal tone) is likely due to a direct consequence of a maturational change in neural regulation of the heart via the vagus and not indirectly due to changes in respiratory rate. In addition, the lack of an effect on heart rate, suggests that the positive impact of FNI on neural maturation of vagal pathways is not dependent on a change in basal metabolic rate.

Results reported here, as expected, showed reliable sleep state-related differences in heart rate and RSA. These findings support the conclusion that the methodologies used in this current study were valid measures of these physiological markers of early autonomic function. To our knowledge, this is the first study to show that the developmental slope for vagal efficiency is greater when infants are in active sleep. These state-related differences in autonomic function, even prior to term age, demonstrate the importance of monitoring sleep state when interpreting measures of autonomic function.

There are several limitations to the assessments made in this current study. The autonomic measures were obtained only during sleep. There are clear advantages to acquiring physiological data when infants are at rest with minimal movement disturbances. However, it would be important to document if the effects of FNI can be demonstrated in awake-infants. In addition, it would also be of interest to monitor the dynamics of autonomic state while being held by their mothers. Based on our theoretical perspective, we would expect that following several weeks of emotional engagement and connection, the vagal effects, which we have reported, would be even more pronounced during periods of maternal contact. This study also did not test our hypothesis that the changes in vagal efficiency we report here after FNI were the result of Pavlovian conditioning or other mechanisms related to an association with a safe and socially/

emotionally engaging parent. With only two points, we could not document whether the effects of the intervention emerged in direct association with intervention sessions. Given the heterogeneity and multiple comorbidities that preterm infants experience, it would not be possible with the available sample size and experimental design to create subgroups based on other clinical features. Such a study could answer the potential role that other clinical conditions play in the sensitivity of the autonomic nervous system to FNI. These important questions would require a large multisite study evaluating several hundred preterm infants to balance the subjects into smaller groups based on other clinical features.

There are additional important aspects to our findings that should be considered further. First, while our measure of vagal efficiency in FNI subjects does increase more rapidly from ~35 weeks PMA to ~41 weeks PMA, the values at ~35 weeks are lower in FNI with no group difference apparent near-to-term age. The average age at birth in these subjects was ~30 weeks PMA and the intervention began, on average, at ~1 week after birth. All FNI infants had received at least some intervention prior to the assessments at ~35 weeks. Thus, it may be possible that there is a biphasic response to the intervention with an initial effect of decreasing vagal tone and vagal efficiency followed by a period during which the intervention promotes more rapid increases. Although we would predict that FNI infants would continue on this more rapid increase trajectory, we do not have repeated assessments during the early post-discharge period to evaluate this hypothesis. Another alternative might be that in SC infants one of the effects of stress associated with preterm delivery and NICU hospitalization is that for some period of time after birth, these stressors accelerate maturation of parasympathetic, and possibly other systems. But, for FNI infants, the effects of these stressors are buffered by the intervention and thus, at ~35 weeks PMA SC infants have higher vagal tone and efficiency than FNI. With extension of the NICU stay, the effects of the NICU stressors began to diminish, either due to "burn out" or perhaps adaptation. In FNI infants, the early buffering of effects of stress continue and are then over taken by promotion of maturation associated with the benefits of physiological and emotion connection mediated by the intervention. These hypotheses, while plausible, will be difficult to test. But, in ongoing replication trials (NCT03267043; NCT02710474; NCT03442439), as well as a trial in preschool age children (NCT03442439), we are obtaining data about emotional connection repeatedly throughout the NICU stay using the Welch Emotional Connection Screen, a newly developed screener for emotional connection (Hane et al., 2018). We hypothesize that the time course of increases in emotional connection will parallel changes in autonomic measures and thus inform to some extent this unexpected pattern in physiological change. Finally, we are aware that accelerated maturation in some systems may not always be beneficial as there can be mismatch among multiple system capabilities. Moreover, rapid developmental increases may not always be related to rapid maturation but rather reflect ongoing stress. Keeping these alternatives in mind is of course critically important when evaluating and interpreting any developmental intervention.

In conclusion, this study supports the role of FNI in enhancing the development of autonomic regulation in preterm infants. The values of RSA and vagal efficiency observed at near term in FNI infants were similar to prior values for RSA and vagal efficiency measured in full term infants (Porges et al., 1999). These findings suggest that FNI promotes normalization in maturation in these systems. The results presented here also enrich our understanding of how FNI might mediate long-term beneficial outcomes by drawing upon both the polyvagal theory (Porges, 1995; Porges et al., 1996) which provides an understanding of how autonomic states are a neurophysiological platform for optimal co-regulation between infant and caregiver, and calming cycle theory (Welch, 2016; Welch & Ludwig, 2017b; Welch & Ludwig, 2017b) which provides a model for understanding how repeated, calming, co-regulatory mother/infant interactions positively reinforce and condition approach, prosocial autonomic states. By combining these ideas, a new theory of change for the lasting impact of FNI emerges. In this way, facilitating mother/infant physiological co-regulation and emotional connection in the NICU is a practicable and effective means of optimizing postnatal development of autonomic regulation and neurobehavioral outcomes in preterm infants.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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