Family Nurture Intervention in the Neonatal Intensive Care Unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial

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Background: Preterm infants are at high risk for adverse neurodevelopmental and behavioral outcomes. Family Nurture Intervention (FNI) in the Neonatal Intensive Care Unit (NICU) is designed to counteract adverse effects of separation of mothers and their preterm infants. Here, we evaluate effects of FNI on neurobehavioral outcomes. **Methods:** Data were collected at 18 months corrected age from preterm infants. Infants were assigned at birth to FNI or standard care (SC). Bayley Scales of Infant Development III (Bayley-III) were assessed for 76 infants (SC, $n = 31$; FNI, $n = 45$); the Child Behavior Checklist (CBCL) for 57 infants (SC, $n = 31$; FNI, $n = 26$); and the Modified Checklist for Autism in Toddlers (M-CHAT) was obtained for 59 infants (SC, $n = 33$; FNI, $n = 26$). **Results:** Family Nurture Intervention significantly improved Bayley-III cognitive ($p = .039$) and language ($p = .008$) scores for infants whose scores were greater than 85. FNI infants had fewer attention problems on the CBCL ($p < .02$). FNI improved total M-CHAT scores ($p < .02$). Seventy-six percent of SC infants failed at least one of the M-CHAT items, compared to 27% of FNI infants ($p < .001$). In addition, 36% of SC infants versus 0% of FNI infants failed at least one social-relatedness M-CHAT item ($p < .001$). **Conclusions:** Family Nurture Intervention is the first NICU intervention to show significant improvements in preterm infants across multiple domains of neurodevelopment, social-relatedness, and attention problems. These gains suggest that an intervention that facilitates emotional interactions between mothers and infants in the NICU may be key to altering developmental trajectories of preterm infants. **Keywords:** Nurture, intervention, Bayley, M-CHAT.

Introduction

Advances in prenatal and neonatal care have led to increased survival of preterm infants (Hack, Klein, & Taylor, 1995). However, infants born prematurely continue to be at risk for a broad range of adverse short- and long-term outcomes (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Moster, Lie, & Markestad, 2008). These include impairments in language (Rand & Lahav, 2014; Van Noort-Van Der Spek, Franken, & Weisglas-Kuperus, 2012), attention (Hall et al., 2008) and executive function (Baron, Kerns, Muller, Ahronovich, & Litman, 2012; Peterson et al., 2000; Sun & Buys, 2012). As many as 30% of infants born <1000 g have impaired cognitive development at follow-up (Belfort, Santo, & McCormick, 2013). Maladaptive social-relatedness and communication delays are also characteristic of children born prematurely (Boyd et al., 2013; Lindstrom, Lindblad, & Hjern, 2011; Mahoney, Minter, Burch, & Stapel-Wax, 2013; Ritter, Perrig, Steinlin,

& Everts, 2014). These characteristics are core deficits associated with Autism Spectrum Disorder (ASD). A recent long-term study of preterm infants found that by early adulthood the entire cohort had an estimated 5 per 100 prevalence of ASD (Pinto-Martin et al., 2011). Among studies looking at the behavior of preterm infants between the ages of 18–24 months corrected age (CA), one reported that 25% showed risk for ASD using the Modified Checklist for Autism in Toddlers (M-CHAT; Limperopoulos et al., 2008). Another reported that 40% of the infants showed risk for ASD using the Quantitative Checklist for Autism in Toddlers (Q-CHAT; Wong, Huertas-Ceballos, Cowan, & Modi, 2014).

Many pre- and postnatal factors may contribute to adverse outcomes in prematurely born infants: maternal and fetal health, neonatal intensive care unit (NICU) ecology, and interruption of intrauterine development. Additionally, early maternal separation has long been known to have profound short- and long-term adverse effects (Barrett & Fleming, 2011). NICU care of preterm infants inherently involves prolonged periods of physical and emotional separation. This

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separation interferes with patterns of mother–infant interaction that normally include physical contact, verbal soothing, breast feeding, odor and heat exchange, and eye contact. In animal models, maternal separation alters stress responsivity (Gutman & Nemeroff, 2002; Levine, 2005) as well as cognitive, social, and emotional function (Romeo et al., 2003; Schmauss, Lee-Mcdermott, & Medina, 2014). Moreover, lower quality and quantity of maternal care has been linked to heightened stress reactivity and impaired social interaction in animal studies (Liu et al., 1997; Menard & Hakvoort, 2007; Parent & Meaney, 2008) and human studies (Hane & Fox, 2006; Hane, Henderson, Reeb-Sutherland, & Fox, 2010).

Early intervention has long been considered crucial for reducing the severity of neurodevelopmental disorders (Vanderveen, Bassler, Robertson, & Kirpalani, 2009). Several NICU interventions aim to improve neurodevelopmental outcomes of premature infants: Newborn Developmental Care and Assessment Program (NIDCAP; Als et al., 1994, 2012); skin-to-skin care (Conde-Agudelo, Belizan, & Diaz-Rossello, 2011; Feldman, Eidelman, Sirota, & Weller, 2002); massage therapy (Field, 2010; Field, Diego, Hernandez-Reif, Deeds, & Figuereido, 2006; Vickers, Ohlsson, Lacy, & Horsley, 2004); and exposure to adult language (Caskey, Stephens, Tucker, & Vohr, 2014). These interventions have produced mixed results for outcomes beyond 12 months of age (Conde-Agudelo et al., 2011; Ohlsson & Jacobs, 2013; Symington & Pinelli, 2006). Despite emphasis on early intervention, treatments for social-relatedness problems, including ASD, are typically initiated at 2–4 years (Bradshaw, Steiner, Gengoux, & Koegel, 2015), rather than at birth.

Family Nurture Intervention (FNI) is a new intervention designed to overcome the maladaptive conditioning effects of maternal separation and the NICU environment on the premature infant. It is hypothesized to do so by facilitating an emotional connection and by establishing an adaptive classical homeostatic conditioning routine between mother and infant, referred to as the *Calming Cycle* (Welch, 1988; Welch, Hofer, Brunelli, Stark, et al., 2012). A randomized controlled trial (RCT) of the intervention was conducted between 2008 and 2012 (Welch et al., 2013, 2014, 2015). The current study is a longitudinal follow-up of secondary outcomes, as measured by the Bayley Scales of Infant Development (3rd edition; Bayley-III), the Child Behavior Checklist (CBCL; Achenbach, 1992), and the M-CHAT, at 18 months CA. Results show that FNI led to significant improvement in all three.

Methods
Trial design and participants

Data were collected as part of a RCT in the NICU of Morgan Stanley Children's Hospital of New York at Columbia University Medical Center (Welch, Hofer, Brunelli, Andrews, et al., 2012; Welch, Hofer, Brunelli, Stark, et al., 2012; Welch et al., 2013). The registered trial (ClinicalTrials.gov; NCT01439269) was approved by the Medical Center's Institutional Review Board. Written informed consent was obtained from mothers prior to group assignment. The primary outcome of this trial, safety and feasibility of this intervention, has been reported with adherence to the CONSORT 2010 guidelines (Welch et al., 2013).

Participants included mothers who had recently given birth to a singleton or twins between 26 and 34 weeks gestational age. Exclusions were: major congenital defects; birth weight < third percentile; maternal age <18 years; mother not fluent in English; mother reported current or prior mental illness, addiction, or substance abuse; and mother did not have another adult in her home.

A total of $N = 115$ mothers of $N = 150$ infants were enrolled and randomized by block design to receive either FNI or Standard Care (SC). Blinding of study staff was not possible as these individuals needed to identify subjects in the intervention group to administer FNI and collect certain data. FNI Nurture Specialists, who were trained NICU nurses, facilitated the intervention with mothers in the FNI group ($N = 59$). Mothers assigned to the SC group ($N = 56$) did not meet with Nurture Specialists, but received standard of care typical for a NICU-hospitalized infant, including contact with medical staff, bedside nursing staff, a psychologist, a social-worker, and special parenting groups. Research assistants met with SC mothers to obtain questionnaires once weekly over the course of their NICU stay. Although SC mothers were in close proximity to FNI mothers and were aware that they were taking part in an RCT involving two groups, the NICU allowed for a high degree of privacy and SC mothers were not explicitly informed about the FNI procedures by study staff. Generally, the NICU census was 60–80 infants. Typically, there were fewer than three study mothers in the NICU at any one time, which we believe limited the chances of communication between groups. Nonetheless, mothers in the SC group were able to engage in nurturing activities of their choosing, which in our trial included skin-to-skin or non-skin-to-skin holding. While these activities were optional and not documented by study staff, they were self-reported in activity logs. Occasionally, SC mothers expressed regret at their group assignment and one SC mother tried the scent cloth exchange with her infant. Infants in both groups were assessed for electroencephalographic, autonomic, and behavioral function at several time points.

Only infants who completed at least one of the three assessments were included (Bayley-III: SC $N = 31$, FNI $N = 45$; CBCL (1.5–5): SC $N = 31$, FNI $N = 26$; M-CHAT: SC $N = 33$, FNI $N = 26$, Figure 1). Four SC infants had a Bayley-III, but no M-CHAT, and six SC infants had an M-CHAT, but no Bayley-III. In contrast, 19 FNI infants had a Bayley-III, but no M-CHAT, and none had an M-CHAT, but no Bayley-III. Some mothers failed to complete the M-CHAT because their infants (seven FNI, one SC) were enrolled in other studies with testers not involved in the present study and who did not ask mothers to complete forms during their visit. Nine of the remaining FNI infants and two SC without completed M-CHATs were twins for whom time constraints precluded M-CHAT completion. Although more SC infants completed the M-CHAT, FNI infants with no M-CHAT scored seven points higher on the Bayley-III cognitive subscale than SC infants. Further, cognitive scores of FNI infants who did and did not complete an M-CHAT were within one point of each other. Thus, there was no apparent bias in M-CHAT results due to this imbalance.

Family Nurture Intervention: activities and procedures

Nurture Specialists facilitated FNI during mother–infant sessions at the earliest time possible after delivery (mean of
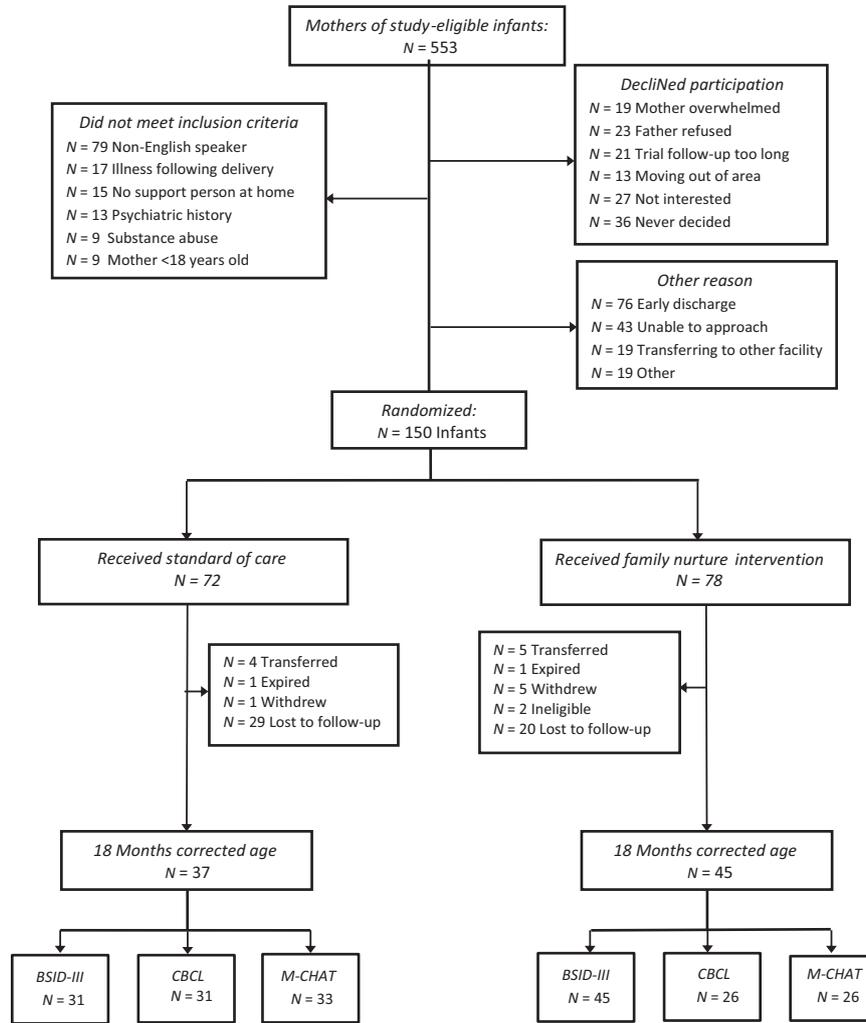
Figure 1 Consort diagram

7 days; Welch, Hofer, Brunelli, Stark, et al., 2012; Welch et al., 2013). Nurture Specialists met with FNI mothers an average of 6.4 hr/week to facilitate calming sessions. Initial sessions took place while infants were confined to the isolette. The first FNI activity was scent cloth exchange; the mother wore one cloth in her brassiere and the other was placed under her infant's head. At each visit, the infant received the mother's cloth and the mother received the infant's cloth. Nurture Specialists instructed mothers to use gentle but firm and sustained touch, to speak to their infants about their feelings in their native language, and to engage in as much eye contact as possible. Further, the above activities were incorporated into skin-to-skin and non-skin-to-skin holding once infants were stable enough to be removed from the isolette.

The RCT protocol minimized the possibility that FNI effects were attributable to nonspecific attention paid to FNI mothers by having both FNI and SC mothers agree to meet four times per week with study staff. During individual meetings, study staff assisted all mothers with filling out questionnaires that quantified time spent with their infants in various 'nurturing' activities. Explanations and administration of the outcome test procedures were given identically to both groups.

Assessments. At 18 months CA, the Bayley-III was administered by a certified, blinded psychologist and mothers completed the CBCL 1.5–5 and M-CHAT questionnaires.

Bayley-III: The Bayley-III is a standardized, validated assessment of infant development between 1 and 42 months

of age that assesses three developmental domains: cognitive (sensorimotor development, exploration and manipulation, object relatedness, concept formation, and memory), language (receptive and expressive), and motor (gross and fine motor; Johnson & Marlow, 2006). For each domain, a composite score is provided and is scaled to a mean score of 100 and standard deviation of 15. Scores <70 indicate significant developmental delay and scores <85 indicate mild to moderate developmental delay (Vohr et al., 2012).

Child Behavior Checklist (1.5–5): The CBCL is a widely used parent-report assessment of behavior problems in children aged 18 months to 5 years (Achenbach, 1992). Parents rate their child's behavior on 99 items using the following scale: 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true; a higher score indicates the presence of problematic behavior. The instrument is standardized to measure a child's behavior along two axes (externalizing and internalizing) and seven subscales (emotional, somatic, withdrawn, attention, sleep, anxiety, and aggression; Cosentino-Rocha, Klein, & Linhares, 2014).

Modified Checklist for Autism in Toddlers: The M-CHAT is a parent-report questionnaire containing 23 items related to sensory responsiveness, language and communication, and nonverbal social communication that screen children 16–30 months of age for autistic traits (Robins, Fein, Barton, & Green, 2001). Parents designate 'yes' or 'no' to indicate whether the statement is true of their child. If a parent answers an item

in a way that indicates risk, the infant is considered to have failed that item. A total score of 0–2 demonstrates minimal risk, while a total score of 3–6 suggests that the child be followed and reevaluated, and a total score of 7–23 supports referral for intervention.

Covariate analyses. Bayley-III: We first determined the contributions of nine possible covariates of the cognitive, language, and motor subscales of the Bayley-III: sex, birth weight (BW), twin status, mother's age, mother's level of education (completed at least an associate's degree or not), whether or not the household was bilingual, whether or not the mother had a partner (married or not) living with her, whether or not there were children other than the study infant(s) living in the home. The ninth possible covariate was tester/test condition. Although all 76 Bayley-III assessments were administered by testers who were blind to group assignment, 65 were administered by a single, study-associated tester and were filmed in a follow-up clinic. The other nine infants were enrolled in the other NICU studies and were assessed by one of the four other testers who were not associated with this study. These assessments were conducted without filming at various locations.

Three stepwise regression analyses determined which, if any, of the nine possible covariates were related to the Bayley-III subscales. Variables with p-values <.10 were then included as covariates in a second series of multiple regression analyses in which these variables were correlated with the subscale scores. Residuals from these analyses were then added to raw means to compute adjusted cognitive, language, and motor scores.

Cognitive scores were adjusted for sex (females scored higher than males, $\beta = 11.5$, $p = .001$), mother's education (higher scores with greater education, $\beta = 11.3$, $p = .011$), and tester/test conditions (higher scores by majority tester, $\beta = -14.3$, $p = .004$). Language scores were adjusted for sex ($\beta = 17.6$, $p < .001$), mother's education ($\beta = 12.0$, $p = .016$), and BW ($\beta = 8.7$ points/kg, $p = .057$). Motor scores were adjusted for sex ($\beta = 6.8$, $p = .009$), mother's education ($\beta = 6.6$, $p = .043$), and tester/test conditions ($\beta = 12.6$, $p = .001$). Effects of the intervention were then evaluated on t-tests to compare the means of SC versus FNI or, in some cases, χ^2 to compare the number of SC versus FNI cases within defined limits.

The computation and analyses of adjusted CBCL and total M-CHAT scores followed a similar approach except tester/test condition was not included as a covariate as these measures were always obtained by study staff.

Child Behavior Checklist 1.5–5: Child Behavior Checklist subscale scores and total scores were adjusted for the following covariates, where $p < .10$: Mother's education (attention: $\beta = -1.672$, $p = .002$, emotion: $\beta = -.990$, $p = .074$, aggression: $\beta = -3.775$, $p = .014$, withdrawn: $\beta = -2.020$, $p = .001$, sleep: $\beta = -1.217$, $p = .095$, somatic: $\beta = -2.013$, $p = .001$, anxiety: $\beta = -2.061$, $p = .001$, total score: $\beta = -21.573$, $p < .001$); Mother's age (emotion: $\beta = -.070$, $p = .088$, aggression: $\beta = -.446$, $p = .010$, sleep: $\beta = -.099$, $p = .065$, total score: $\beta = -1.133$, $p = .009$); Sex (aggression: $\beta = -3.775$, $p = .014$, somatic: $\beta = -.945$, $p = .010$, total score: $\beta = -7.654$, $p = .055$); Twin status (emotion: $\beta = .646$, $p = .008$, anxiety: $\beta = .686$, $p = .014$), BW (withdrawn: $\beta = -.001$, $p = .020$); Partner status (attention: $\beta = -1.381$, $p = .067$); Other Children living in the home (aggression: $\beta = -.446$, $p = .010$).

Modified Checklist for Autism in Toddlers: M-CHAT total scores were adjusted for Mother's education ($\beta = 1.790$, $p = .018$) and BW ($\beta = .032$, $p = .063$).

Results

Demographics and clinical characteristics

We compared family demographics and infant clinical characteristics at enrollment for those who did and did not return for at least one of the three assessments (Bayley-III, CBCL, M-CHAT; Table S1, available online). These include mother's age, education, parity, partner status, and bilingualism, and infant's gestational age, BW, sex, twin status, CPAP, and Apgar score. There are no significant group differences in family demographics or infant clinical characteristics at enrollment, nor at 18 months for those who returned for at least one of the three assessments. For both groups, mothers who returned for at least one of the assessments were more likely to have an associate's degree or higher compared to mothers who did not return ($p = .025$). Therefore, degree of education was included as a covariate for all analyses. All other comparisons between those who did and did not return were not statistically significant ($p > .05$).

Bayley-III

Although initial analyses of adjusted Bayley-III scores revealed no significant effects of FNI (Figure 2A–C), after scores were fit to normal curves, the distributions suggested a rightward shift among FNI infants (Figure 2D–F). We explored intervention effects on Bayley-III scores using a cut-off of 85 (1*SD* below the mean) as used by Nordhov and colleagues in their preterm intervention evaluation (Nordhov et al., 2010). This cut-off has been used to indicate mild to moderate developmental delay (Johnson, Moore, & Marlow, 2014; Vohr et al., 2012). For infants scoring >85, FNI significantly increased cognitive scores by 6.0 points (Cohen's $d = .37$ $p = .039$) and language scores by 8.2 points (Cohen's $d = .45$ $p = .008$). The increase in motor scores of 3.8 points did not reach significance (Cohen's $d = .30$, $p = .061$; Figure 2G–I).

Child Behavior Checklist (1.5–5)

CBCL scores revealed significant group differences in attention problems ($p = .028$) with an effect size of 0.51 (Table 1).

M-CHAT

Total M-CHAT scores were adjusted for effects of BW ($p = .032$) and mother's education ($p = .072$). FNI infants failed significantly fewer M-CHAT items than SC infants (total score: SC, 2.0 ± 0.5 vs. FNI, 0.5 ± 0.2; Cohen's $d = 0.62$, $p < .02$).

We compared groups using four analyses: (a) 'failed any item'; (b) 'failed any critical item'; (c) 'failed two or more critical items'; (d) 'failed any three
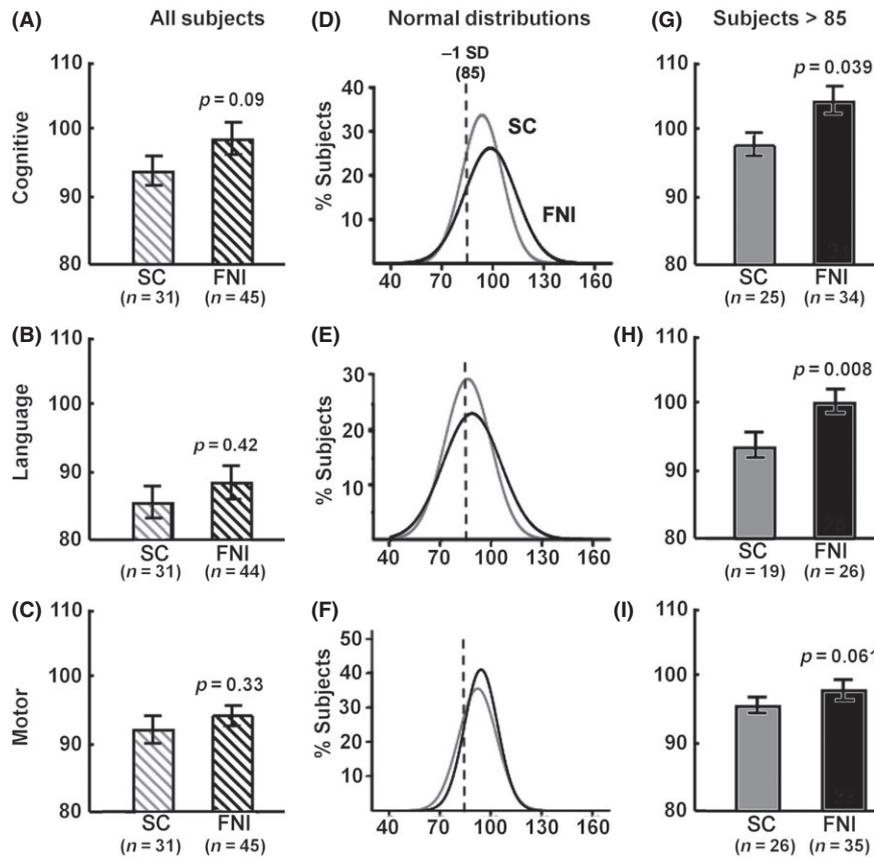
Figure 2 Adjusted cognitive, language, and motor Bayley-III scores at 18 months CA follow-up. (A–C) No significant effects of the intervention were seen when comparing the scores of all subjects. (D–F) Scores for each study group and each Bayley-III subscale were fit to a normal curve. The SC and Family Nurture Intervention (FNI) groups were very similar for infants with scores that were ≤ 85, or 1 standard deviation (SD) below the mean (vertical dashed lines). However, the FNI distributions for the cognitive and language scales were right-shifted. (G–I) In subjects with scores >85, FNI significantly increased the cognitive scores by 6.0 units ($p = .039$), and language scores by 8.2 units ($p = .008$). The increase in motor scores by 3.8 units did not reach significance ($p = .061$)

Table 1 Child Behavior Checklist (1.5–5) scores at 18 months corrected age for Standard Care (SC) and Family Nurture Intervention (FNI) infants. See Methods for applicable covariates

Syndrome Scales	SC ($n = 31$)	FNI ($n = 26$)	p	Cohen's d
Attention	1.8 ± 0.2	1.0 ± 0.3	.03	.51
Emotion	1.1 ± 0.2	0.9 ± 0.3	.61	.13
Aggression	6.8 ± 0.9	5.6 ± 1.0	.39	.19
Withdrawn	0.9 ± 0.2	0.6 ± 0.2	.40	.23
Sleep	2.2 ± 0.3	1.7 ± 0.3	.25	.26
Somatic	1.0 ± 0.2	1.1 ± 0.4	.69	.07
Anxiety	1.8 ± 0.3	1.2 ± 0.3	.14	.56
Total Score	22.4 ± 2.5	17.7 ± 2.7	.22	.26

items.' Fewer FNI (27%) than SC infants (76%) failed any M-CHAT item ($p < .001$, Table 2). Based on six critical items identified by discriminant functional analysis (DFA) that predicted the total score (Robins et al., 2001), our results showed that none of the FNI infants failed any of these items, whereas 21% of SC infants failed at least one critical item ($p < .02$, Table 2).

The M-CHAT provides two criteria for referral; 'failed any three or more items' and 'failed two or more critical items' (Robins et al., 2014). We found 21% of SC and 8% of FNI infants failed any three or more items ($p < .2$, Table 2). Additionally, six SC

infants (18%) failed two or more critical items, but no FNI infants did so ($\chi^2 = 5.26$, $p < .03$, Table 2).

In Table 3, we divided items into three categories: six sensory and motor; 14 communication and social-relatedness; and three uncategorized. All of the 'DFA-6' critical items address communication and social-relatedness function, as opposed to sensory and motor function. Twelve SC infants (36%) had at least one failure in the communication/social-relatedness domain versus no FNI infants ($\chi^2 = 11.87$, $p < .001$). Eighteen SC infants (55%) had at least one failure in sensory and motor items, compared to 6 (23%) FNI infants ($\chi^2 = 5.97$, $p < .02$).

Table 2 Modified Checklist for Autism in Toddlers score analyses

	SC	Family Nurture Intervention	χ^2	p
Failed any item	75.8% (25 of 33)	26.9% (7 of 26)	13.97	<.001
Failed any DFA-6 critical items	21.2% (7 of 33)	0% (0 of 26)	6.26	<.02
Failed two or more DFA-6 critical items	18.2% (6 of 33)	0% (0 of 26)	5.26	<.03
Failed any three or more items	21.2% (7 of 33)	7.7% (2 of 26)	2.06	<.20

Table 3 The 23 Modified Checklist for Autism in Toddlers (M-CHAT) items and the number and % of SC and Family Nurture Intervention (FNI) infants who failed each item. Items segregate into sensory-motor or social-relatedness/competency domains. Dotted lines denote items that do not clearly fit into either of these two domains. Notably, prior discriminant functional analysis identified six items ('DFA-6' in bold) that predict total M-CHAT score that are all social-relatedness

M-CHAT Items	Functional Domain	SC n (%)	FNI n (%)
1. Does not enjoy being swung	Sensory-motor	0 (0)	0 (0)
2. Does not take interest in others	**Social-related**	**1 (3)**	**0 (0)**
3. Does not like climbing on things	Sensory-motor	2 (6)	1 (4)
4. Does not enjoy playing peek-a-boo	Social-related	1 (3)	0 (0)
5. Does not pretend	Social-related	3 (9)	0 (0)
6. Does not point to ask for something	Social-related	4 (12)	0 (0)
7. Does not point to indicate interest	**Social-related**	**3 (9)**	**0 (0)**
8. Does not play properly with small toys	Sensory-motor	4 (12)	1 (4)
9. Does not bring objects to show you	**Social-related**	**1 (3)**	**0 (0)**
10. Does not look you in the eye	Social-related	2 (6)	0 (0)
11. Is oversensitive to noise	Sensory-motor	6 (18)	3 (12)
12. Does not smile in response to your face or smile	Social-related	0 (0)	0 (0)
13. Does not imitate you	**Social-related**	**5 (15)**	**0 (0)**
14. Does not respond to name when you call	**Social-related**	**0 (0)**	**0 (0)**
15. Does not look at toy when you point to it	**Social-related**	**2 (6)**	**0 (0)**
16. Does not walk	Sensory-motor	3 (9)	1 (4)
17. Does not look at things you are looking at	Social-related	3 (9)	0 (0)
18. Makes unusual finger movements near face	Sensory-motor	12 (36)	4 (15)
19. Does not try to attract your attention to activity	Social-related	4 (12)	0 (0)
20. You have wondered if your child is deaf	------	2 (6)	1 (4)
21. Does not understand what people say	------	0 (0)	0 (0)
22. Stares at nothing or wanders with no purpose	------	4 (12)	2 (8)
23. Does not look at your face for reaction	Social-related	3 (9)	0 (0)

FNI effects on M-CHAT and CBCL are not dependent on Bayley-III

There were nonsignificant negative correlations between total M-CHAT score and the Bayley-III language and motor subscales ($r = -.18$, $p > .2$; $r = -.22$, $p > .1$, respectively). Although cognitive scores on the Bayley-III were significantly correlated with total M-CHAT score ($r = -.33$, $p < .02$), the effect of FNI on lowering M-CHAT scores remained significant when cognitive, language, or motor scores were included as covariates (p-values < .025, <.02 and <.02, respectively). Similarly, FNI effects on the CBCL attention scale remained significant when cognitive, language, or motor scores were included as covariates (p-values < .015, <.015 and <.015, respectively).

Breast feeding, breast milk, skin-to-skin, or clothed holding do not mediate the effects of FNI

Four variables recorded during the NICU stay were considered as possible mediators of effects of FNI on Bayley-III, M-CHAT, and CBCL scores: any occur-rence of breast feeding, percent of total volume of feeding that was breast milk, average hours per week of clothed holding, and average hours per week of skin-to-skin holding. The occurrence of breast feeding one time was not different between groups (SC, $28 \pm 6\%$ vs. FNI, $35 \pm 5\%$). The amount of expressed breast milk as a percentage of total feeding was also not different between groups (SC, $56 \pm 5\%$ vs. FNI, $56 \pm 4\%$). The average weekly hours of clothed holding was not different between groups (SC, 3.1 ± 0.4 vs. FNI, 2.5 ± 0.4). Only skin-to-skin holding differed between groups; as previously reported, FNI mothers engaged in skin-to-skin holding ~3 times more than SC mothers (SC, 0.9 ± 0.3; FNI, 2.6 ± 0.2 hr/week, $p < .001$; Welch et al., 2013). However, effects of FNI on Bayley-III cognitive, language, and motor scores (>85) were significant even when controlling for skin-to-skin holding (ANCOVAs: $p < .015$, $p < .002$, $p < .005$, respectively). Similarly, the effects of FNI on the percent of subjects who failed any M-CHAT items remained significant after accounting for the amount of skin-to-skin holding ($p < .01$). The ANCOVA results for CBCL attention scores suggest that

skin-to-skin care may, to some extent, mediate the effects of FNI on the attention subscale because the *p*-value for intervention effects changed from 0.028 to 0.23 when skin-to-skin care was added as a covariate.

Discussion

We examined effects of FNI on neurodevelopmental outcomes at 18 months CA. Results support our overall hypothesis that establishing a *calming cycle* routine with emotional connection between mothers and premature infants in the NICU improves neurodevelopmental and socioemotional functioning in toddlers.

Analysis of Bayley-III cognitive and language scores of infants scoring >85 revealed that FNI infants performed significantly better than SC infants. The lack of intervention effect for those scoring <85 may reflect the presence of medical complications not excluded by our recruitment criteria. These infants may require a different intervention, more FNI than the 6 hr/week administered in this study, or FNI at a later stage of development. It is also possible that effects of FNI on these infants may emerge at a later time, as shown by two prior studies. In one, neurobehavioral scores of prematurely born infants normalized only 3–4 years after the intervention (Rauh, Achenbach, Nurcombe, Howell, & Teti, 1988). In a more recent report, skin-to-skin care did not show a positive effect on executive function at age 5, but did at age 10 (Feldman, Rosenthal, & Eidelman, 2014).

This is the first NICU RCT to use the M-CHAT as an outcome measure. M-CHAT total scores and reevaluation criteria accurately predict subsequent ASD symptom development (Robins et al., 2001). Using the M-CHAT assessment, Limperopoulos (Limperopoulos et al., 2008) reported that 25% of a preterm infant cohort met reevaluation criteria. This is similar to that found for SC infants (21.2% met criteria by failing ≥ 3 items and 18.2% met criteria by failing ≥2 critical items). However, the percent of FNI infants who met reevaluation criteria was significantly below expectation for a preterm population; only 7.7% met reevaluation criteria by failing ≥3 items and 0% met reevaluation criteria by failing ≥2 critical items. Remarkably, no FNI infants, even those who scored <85 on the Bayley-III, failed a social-relatedness item. FNI infants also failed significantly fewer M-CHAT sensory-motor items. These results confirm that FNI had a positive impact on social-relatedness and sensory-motor function at 18 months. Deficits in social-relatedness and sensory processing are likely to place a large number of toddlers born prematurely at risk for other emotional, behavioral, and developmental disorders, in addition to ASD. However, effects of FNI on M-CHAT social-relatedness were not dependent upon better functioning in measures assessed by the Bayley-III, suggesting that while FNI affected both cognition and social functioning, the

mechanisms underlying these effects may be different. Most important, however, FNI improved *both*.

Analysis of CBCL results showed that FNI significantly improved attention scores at 18 months, which is important because attention deficits in preterm infants are highly prevalent and are the first CBCL impairments to be recognized by age 2 (Cosentino-Rocha et al., 2014). The group effect on attention scores became nonsignificant when we added skin-to-skin holding as a covariate, suggesting that skin-to-skin holding may be an independent mediator of attention later in development.

We believe that FNI represents a theoretical and therapeutic advance for NICU care. The results reported in this study may be mediated by classical conditioning of homeostatic mechanisms embedded in mother–infant interactions (Hofer, 1994). Hormonally and sensorially mediated cyclical adaptive care-giving activities are evolutionarily conserved to positively condition an emotional connection between mother and infant (Gonzalez-Mariscal & Rosenblatt, 1996). In this study, we hypothesize that these activities condition the infant to positively respond to the mother, which in turn may condition optimal sympathetic and parasympathetic equilibrium in the infant. Preterm birth disrupts these mechanisms, which can lead to maladaptive emotions and behaviors (Numan, Fleming, & Levy, 2006). We posit that FNI-mediated conditioning accounts for higher responsiveness of the mother to the infant prior to discharge (Hane et al., 2015) and for greater brain activity near to term age (Welch et al., 2014). The 18-month findings presented here are evidence of lasting effects of this nurture-based intervention.

Our results support the idea that the efficacy of FNI may be qualitative, rather than quantitative. Group differences in Bayley-III cognitive scores and M-CHAT 'any fail' scores remained significantly different, even after accounting for variation in the amount of skin-to-skin care. This, coupled with the relatively low 'dose' of the intervention (~6 hr/week), suggests that FNI effects may result from changes in the 'quality' of mother and infant interaction, as opposed to the 'amount' of any activity.

One limitation of the present study is the small sample size at the 18-month follow-up. In addition, our eligibility criteria may not allow for generalization of these findings to mothers and infants with more complicated medical histories, cultural backgrounds, or family systems. Finally, this trial was limited to assessing intervention efficacy. Additional trials are necessary to determine the effectiveness of the intervention to answer, for example, if it is feasible to incorporate FNI into standard NICU care, although this is indicated by our primary outcome paper (Welch et al., 2013).

Currently, the main focus of NICU care is on infant survival. However, medical care alone will not improve long-term emotional, behavioral, and

developmental outcomes in preterm infants. It is now widely recognized that social stimulation in the context of mother–infant interactions is a key component of optimal development (Barrett & Fleming, 2011; Holditch-Davis et al., 2014; Sale, Berardi, & Maffei, 2014). However, families remain an under-utilized resource for infant care, although mothers with appropriate support can provide the type of sensory and emotional input required for healthy development (Jiang, Warre, Qiu, O'Brien, & Lee, 2014). Our findings suggest that long-term outcomes of both neurodevelopment and social-relatedness can be improved by integrating emotional and physiological coregulation between mother and infant into standard care.

Conclusion

This study advances the field of nurture-based interventions in the NICU in important ways. While FNI incorporates some activities that are part of other nurture-based interventions, such as skin-to-skin care and infant touch, this study provides support for integrating these activities into a program of standard NICU care focused on mother–infant connectedness. This is the first NICU RCT to show improvement across multiple domains in preterm infants at 18 months CA. The positive effect of FNI on behavioral problems, social-relatedness, and cognitive and language performance suggests that this intervention may protect against a broad range of developmental delays and disorders.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Enrollment family demographics and infant clinical characteristics, by clinical trial group.

Appendix S1. Consort checklist.

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Key points

- Prematurely born infants are at risk for emotional, behavioral, and developmental disorders.
- Family Nurture Intervention (FNI) is a new approach to facilitate communication and coregulation between mothers and infants in the NICU.
- At 18 months CA, FNI infants have improved neurodevelopment outcomes (Bayley-III).
- The intervention also improved social-relatedness (M-CHAT) and lowered attention problems on the CBCL.

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