Published in final edited form as:

J Neonatal Nurs. 2018 August ; 24(4): 203–207. doi:10.1016/j.jnn.2017.11.001.

Preterm Neurodevelopmental Outcomes Following Orosensory Entrainment Intervention

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Abstract

Previous research indicates that the NTrainer, a pressurized pacifier programmed to produce pulsed pneumotactile stimulation during gavage feeds, has been found to facilitate non-nutritive suck development and shorten the length of hospital stay when used in the Neonatal Intensive Care Unit (NICU). Four groups of children, including infants of diabetic mothers (IDM), healthy controls (HI), and those with respiratory distress syndrome (RDS), or chronic lung disease (CLD), were randomly assigned to an NTrainer therapy or sham ‘control’ condition when in the NICU. At 30 months of age, 113/223 study participants were assessed using standardized language, motor, and cognitive assessments. No significant group differences were evident between the NTrainer and sham groups in language, motor, or cognitive functioning. The NTrainer did not improve nor adversely impact language, cognition, or motor outcomes.

Keywords

Preterm; orosensory; entrainment; cognitive; language; motor; outcomes; intervention

INTRODUCTION

The advent of new brain science technology has led to an increased understanding as well as discovery of new interventions for children born preterm. Children born preterm display differences in their brain development compared to children born full-term¹ and some

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CONFLICT OF INTEREST

None of the authors have a direct financial conflict of interest to disclose. Dr. Barlow is the inventor of the NTrainer System[®], which is registered and licensed by the University of Kansas to Innara Health, Incorporated (Olathe, KS USA).

differences predict later neurodevelopmental delays.² Approximately 10% of infants are born preterm each year.³ Being born early places them at risk for a number of negative neurodevelopmental outcomes.⁴ Areas impacted negatively include feeding, language, motor, and cognition skills.⁵ With respect to feeding, children born preterm have been found to have impaired oromotor pattern generation.^{6,7} Disorganized non-nutritive sucking as a result of poor oromotor pattern generation is present in infants born preterm.^{8,9,10} In addition, meta-analyses of neurodevelopmental outcomes in children born preterm suggest an increased risk of language, motor, and cognitive delays and disorders.^{11,12,13,14} Language abilities of children born preterm at the end of the second year of life have been found to be highly predictive of language abilities at a later time, suggesting the need for intervention services as early as possible.¹⁵ Kalia and her colleagues¹⁶ report that about 70% of very preterm infants and about 30% of late preterm qualify for early intervention services in one or more developmental domains. They also found that few families pursue these early intervention services after hospital dismissal, suggesting a need for early and effective interventions that might be implemented while the infants and families are still in the NICU.

Supplemental sensory-based interventions across several modalities including auditory, olfactory, and vestibular input have been utilized within the preterm population.^{17,18,19,20} These interventions seek to provide key sensory stimulation for the strengthening of neural pathways during a critical time of neurodevelopment. Children born preterm have been shown to respond positively to olfactory stimulation associated with their mother's breastmilk.¹⁹ Auditory stimulation in the form of lullabies¹⁸ and maternal voice^{17,21} also has yielded positive effects on short-term physiologic outcomes and growth of infants born preterm. Interventions providing vestibular stimulation including rocking²² and gliding²³ have similarly been shown to have therapeutic effects on preterm infants in the NICU.

Multimodal sensory interventions also have been investigated in this population. A multisensory intervention approach referred to as ATVV (auditory, tactile, visual, vestibular)²⁴ has been associated with improved feeding and alertness outcomes as well as decreased NICU stays. Another widely implemented multisensory intervention is Kangaroo Mother Care, which utilizes skin-to-skin contact between caregiver and child and provides the infant with tactile, kinesthetic, auditory, olfactory, and vestibular sensory inputs. The use of Kangaroo Mother Care in the NICU setting has been associated with increased physiologic regulation, improved oxygen saturation levels, and decreased length of NICU stay.²⁵

One new sensory intervention that is gaining favor to promote ororhythmic patterning for non-nutritive suck development in the NICU is the NTrainer.^{26, 27,28} The NTrainer consists of a digitally-controlled pneumatic amplifier and a handpiece attached to a Philips AVENT Soothie[®] silicone pacifier. The NTrainer was developed to provide pulsed orocutaneous stimuli that is programmed to be similar in temporal and frequency dynamics to non-nutritive sucking.^{26, 6, 27} The neurobiological hypothesis underlying the feasibility of the NTrainer for improving the feeding of infants born preterm is that orosensory entrainment of trigeminal primary afferents would facilitate the suck central pattern generator (sCPG) in the brainstem. These premotor internuncial circuits in the brainstem are important for the development of rhythmic motor patterns such as sucking, swallowing (swCPG), and

respiration (rCPG), and may play a role in early vocalization and canonical speech.²⁹ It has been hypothesized that children born preterm may miss out on a critical sensory period of development for oromotor control or have compromised oromotor development as a result of sensorineural deprivation and decreased motor activity.³⁰ The use of orosensory entrainment therapy during gavage feeding in the NICU via the NTrainer increases trigeminal input that may modulate plasticity of pontomedullary and thalamocortical pathways during critical brain development.³¹ The NTrainer has been found to significantly improve the dynamics of non-nutritive sucking for children born preterm with respiratory distress syndrome (RDS) and chronic lung disease (CLD) and decrease the length of hospital stay (LOS) for children born preterm who displayed CLD.³⁰ In a multicenter trial involving 210 preterm infants (26–30.9 weeks of chronological age [GA]), Song et al.³² found that infants randomized to receive NTrainer therapy showed a significant reduction in the number of days to full oral feeds and a significant reduction in LOS when the orosensory entrainment intervention was introduced at approximately 31.8 weeks of post menstrual age (PMA). These results provide strong support for the notion of a critical sensory period for orocutaneous stimulation to accelerate suck and oral feeding skills in preterm. Similarly, Soos and Hamman³³ reported anecdotal evidence of increased non-nutritive sucking pattern, improved sucking strength, increased readiness to feed, and overall increased neurodevelopmental functioning in children who received the NTrainer in their NICU. These results on the efficacy of the NTrainer for feeding are encouraging; however, it is unknown whether the use of the NTrainer positively or negatively impacts other neurodevelopmental outcomes, such as language, motor, or cognitive skills.

In this study, we compared the language, motor, and cognitive skills at a later point in development (i.e., 30 months of age) between children who received the NTrainer in the NICU and those skills of children who did not receive the NTrainer. Our specific research question was “Is there a difference in the language, motor, and cognitive abilities at 30 months of age between children born preterm who received the NTrainer in the NICU compared to children born preterm who did not receive the NTrainer?” We predicted that the children in the NTrainer condition might display greater language, cognition, and motor skills compared to those in the control condition if the NTrainer stimulations led to a benefit in the CPGs and/or related motor systems during a critical period of development. A negative impact of the NTrainer was not anticipated, but could not be ruled out because this type of intervention has not been previously utilized. A finding of negligible difference between the groups would indicate that the NTrainer neither assisted nor harmed language, motor, and/or cognitive outcomes.

METHODS

Study design

This was a follow-up observational study of children born preterm who participated in a randomized controlled blind trial of the NTrainer while in the NICU. The NICUs at the Overland Park Regional Medical Center (Overland Park, KS), and Stormont-Vail Regional HealthCare (Topeka, KS) participated in this study. Both centers provided approval of the NTrainer research, which included written informed consent before the study began. The

research protocol for the initial NTrainer intervention study was approved by the Institutional Review Board at the University of Kansas.

NTrainer protocol

While in the NICU, the infants were randomly assigned to either the NTrainer condition or a sham pacifier control. The protocol included stimulation with either the NTrainer or the sham pacifier three times per day during gavage feedings for nine minutes over a period of two weeks (i.e., approximately 10 days) between 34 and 36 weeks of GA. The infants assigned to the sham condition received the same type of Soothie® pacifier that was on the NTrainer handpiece, however, they did not receive the pulsed orocutaneous stimuli. The infants assigned to the NTrainer condition received gavage feedings during the orocutaneous stimulation. The NTrainer and sham pacifiers were administered by a full-time neonatal nurse at each NICU site. Parents, care-providers administering the NTrainer in the NICU, and examiners of assessment (i.e., nursing care and medical staff) were blind as to the treatment assignment for any given study infant.

NICU participant characteristics

The children in the NTrainer NICU study were born between 23 and 36 weeks of GA ($M = 29.75$, $SD = 3.00$), with a weight between 410 and 3,830 grams ($M = 1,402.54$, $SD = 629.65$). They were divided into four diagnostic categories by the neonatologist: Healthy preterm (HI), infants of diabetic mothers (IDM), infants with chronic lung disease (CLD), and infants with Respiratory Distress Syndrome (RDS). The children with RDS were diagnosed with RDS by x-ray and extended supplementary oxygen up to 36 weeks of GA; whereas, the children diagnosed with CLD had supplementary oxygen beyond 36 weeks of GA. The children in the HI and IDM groups had fewer than five days of supplemental oxygen. The children in the HI group also had no specific diagnosis and were medically stable. Children in the IDM group were born to mothers with diabetes (gestational and other forms). All the children displayed head circumference that was within the 10th to 90th percentiles and passed a hearing examination at the NICU as well. The children's GA and birthweight and their distribution over the diagnostic categories were not different between the NTrainer and control groups (all $p > .05$).

Exclusion criteria for NTrainer participation included presence of intracranial hemorrhage grades III and IV, neonatal seizures, nervous system anomalies, periventricular leukomalacia, necrotizing enterocolitis, chromosomal anomalies or craniofacial malformation, cyanotic congenital heart disease, meningitis, sepsis, gastroschisis, omphalocele, diaphragmatic hernia and/or other major gastrointestinal anomalies, or not ready for oral feeding.

Follow-up assessment procedure

The Institutional Review Board at the University of Kansas approved the follow-up assessment procedures. Parents signed a written informed consent and children completed assent prior to initiation of the follow-up assessment. Parents also completed a questionnaire that inquired about their family information and child's developmental history. Each child was seen for a two-hour session that included snack and play breaks.

The *Test of Expressive Language Development-3*, (TELD-3)³⁴ (i.e., expressive and receptive language) and the *Bayley Scales of Development Inventory-III* (BSDI-III)³⁵ (i.e., fine motor, gross motor, and cognitive subtests) were administered by a trained speech-language pathology graduate student and a certified speech-language pathologist, who were blind to the child's treatment condition (i.e., NTrainer or sham) and initial diagnosis (i.e., HI, CLD, RDS, IDM). The TELD-3 was selected instead of the Bayley-III language subtest, because it took a shorter amount of time to administer. The TELD-3 is one of the few psychometrically reliable and valid standardized tests for toddlers that is not based solely on parent report and provides receptive and expressive scores extending across language areas of semantics, syntax, and morphology. Standardized test scores were computed by an independent scorer who did not conduct the testing. These scores were then checked by another independent scorer for accuracy. Any disagreements were resolved through consensus. Both scorers were blind to the child's treatment condition and initial diagnosis.

Statistical analysis

Descriptive statistics and bivariate tests (i.e., *t*-test, chi-square test) were conducted to summarize all measured variables within and between the NTrainer and sham groups. General linear modeling was used to compare the groups for each of the language, cognitive, and motor outcomes (standardized scores), adjusting for the children's GA and medical diagnosis (i.e., HI, CLD, RDS, IDM).

RESULTS

A total of 223 infants completed the NTrainer study in the NICU (see Figure 1). Of those, 76 had moved or were not able to be contacted with their last given contact information. Of the 147 children whose parents were contacted for participation in the study, 34 children were lost to follow-up after contact and 113 participated in the follow-up study. No significant difference was observed between study participants and non-participants in terms of medical diagnosis (i.e., CLD, HI, RDS, or IDM) ($p = .09$), GA ($p = .43$), and baseline weight ($p = .76$).

Follow-up participants

A total of 113 children participated in the follow-up study (see Table 1). Sixty-seven children received the NTrainer when they were in the NICU and 46 received a control (i.e., sham pacifier). The children were approximately 30 months of age ($M = 29.09$, $SD = 0.24$) for the follow-up assessment. The age at the assessment was not different between the treatment conditions ($p = 0.83$). Of the 113 participants, 58.4% were female, 90.3% were non-Hispanic, and 81.4% were White. Most of their mothers had a high school education (51.4%), followed by those with a Bachelor's degree (26.1%) and those with a graduate degree (22.5%). The children's sex, ethnicity, and race and the mothers' education did not differ between the NTrainer and control groups (all $p > .05$).

Language, cognitive, and motor outcomes

Both the raw and adjusted means of each outcome were highly similar, resulting in no significant group differences in any of the outcomes assessed (all $p > .05$) with small effect sizes (see Table 2).

DISCUSSION

Early intervention for children born preterm is critical for deterring a constellation of later negative outcomes. The NTrainer, a somatosensory method to stimulate oromotor development in the NICU setting, did not lead to gains above and beyond the children in the control group for any of the measures of language, motor, and cognition. Regardless of the child's GA or medical diagnosis, the NTrainer did not positively or negatively impact neurodevelopmental outcomes. The lack of differences between the two groups may be due to several possible explanations. One is related to the dosage, modality, and timing of the intervention, a second to endogenous factors associated with preterm birth, and the third explanation is related to our current understanding of how feeding, language, motor, and cognition develop and operate separately and together.

The dosage explanation would be that the NTrainer intervention was too brief to impact the development of language, cognition, and motor skills. Although, the orosensory entrainment dosage provided has been reported to improve NNS development, improve feeding, and reduce length of stay (LOS) in the NICU;^{27, 28} perhaps a longer period of intervention is needed (i.e., 30–33 weeks PMA) to impact motor, cognition, and language skills. Alternatively, it may be that an earlier period of stimulation is necessary, or there may be a critical time period for such stimulation. Results from Song et al.³² indicate that orosensory entrainment provided at 31^{4/7} to 32^{6/7} PMA of GA resulted significant decreases on the time to full oral feeds, shorter LOS, earlier PMA at full oral feeds, and earlier PMA at hospital discharge.

Use of the NTrainer coupled with sensory stimulation in additional modalities may have potential in increasing long-term neurodevelopmental outcomes. Caregiver talk may in some way facilitate one aspect of development, in particular, that of language development. A recent study found that infants in the NICU who receive more talk from their parent have greater language skills at seven and 18 months of age compared to those who receive less talk.³⁶ Future studies of the NTrainer that incorporate additional sensory modalities, such as caregiver talk, may yield significant findings.

A second possibility is that long-term neurodevelopmental effects are more driven by endogenous factors resulting from preterm birth such as compromised pulmonary systems, cardiac insufficiency, and neural infarcts than exogenous factors such as utilization of therapeutic interventions. This idea is supported by other studies of sensory-based interventions and neurodevelopmental outcomes. Specifically, Nelson et al.³⁷ found that auditory-tactile-visual-vestibular therapy was successful for improving short-term physiological outcomes and shortened NICU stay, but did not find a significant difference between intervention and control conditions when developmental testing was conducted at one year of age. Although Kangaroo Care has been found to improve neurodevelopmental

outcomes up to age 3 months,³⁸ Charpak et al.³⁹ found no difference between treatment and control children at one year of age despite promising initial benefits seen for short-term outcomes. It may be difficult to enact long-term developmental benefits from sensory-based early interventions due to endogenous factors associated with preterm birth.

The third explanation is that our hypothesized relationship between feeding, language, cognition, and motor abilities requires further modification and refinement. Facilitating the organization or reorganization of a preterm oromotor system is evident with the NTrainer,²⁶ yet it was not sufficient to generalize or facilitate other motor and cognitive systems. Very early in development these systems may be dedicated and independent, with unknown degrees of overlap and shared characteristics as the systems develop. Future studies of orosensory entrainment may increase our understanding of these potential hypotheses, by targeting a critical time period for use of the NTrainer as noted by Song et al.³²

CONCLUSIONS

These are the first data of the neurodevelopmental outcomes of children who were born preterm and underwent intervention with the NTrainer in the NICU. Although there were no advantages in language, cognition, or motor skills for those in the intervention group, professionals who utilize the NTrainer have preliminary data that it did not cause harm in these vulnerable infants. Future studies of the NTrainer in conjunction with other sensory modalities and/or within a critical time period will shed light on its usefulness to strengthen neurodevelopmental outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by grants NIH R01 DC003311 (Barlow), NIH P30 HD02528, The Barkley Trust (Barlow), and the Sutherland Family Foundation (Barlow). The authors express thanks to Christine Kosiog and Sarah Orr for experimental support. We also wish to thank the families who participated in this research.

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Figure 1.
Caption. Follow-up population attrition

Table 1

Participant Characteristics

	NTrainer (<i>n</i> = 67)	Control (<i>n</i> = 46)	<i>p</i> ¹	ES ²
Demographic characteristics				
Sex (male: female)	38: 29	28: 18	0.66	0.04
Ethnicity			0.89	0.05
<i>Hispanic or Latino</i>	3	3		
<i>Not Hispanic or Latino</i>	61	41		
<i>Unknown</i>	3	2		
Race			0.63	0.12
<i>Asian</i>	1	0		
<i>Black/African American</i>	3	4		
<i>Multiple</i>	7	6		
<i>White</i>	56	36		
Medical diagnosis in NICU			0.52	0.14
<i>HI</i>	21	15		
<i>CLD</i>	26	19		
<i>RDS</i>	8	8		
<i>IDM</i>	12	4		
Family characteristics				
Maternal education			0.86	0.05
<i>High school</i>	32	25		
<i>Bachelor's degree</i>	18	11		
<i>Graduate degree</i>	15	10		
<i>Missing</i>	2	0		
Birth/Follow-up characteristics				
GA in days	208.50 (21.62)	207.90 (20.38)	0.88	0.03
CA at testing (month)	29.09 (0.25)	29.10 (0.23)	0.83	0.04
Birth weight (gram)	1,394.70 (657.80)	1,413.80 (593.85)	0.75	0.06

¹ *p*-value of *t*-test for continuous variables or chi-square test for categorical variables.

² Effect size: Cohen's *d* for continuous variables or Cramer's *V* for categorical variables.

Note. Mean (standard deviation).

Table 2

Standardized Scores of Language, Cognition, and Motor Skills

	NTrainer	Control	95% CI ¹	d ²	p ³
All (N = 113)					
Language skill					
<i>Receptive score</i>	92.12 (10.47)	92.80 (13.30)	-5.13; -3.76	0.02	0.91
<i>Expressive score</i>	95.12 (6.89)	95.93 (7.37)	-3.51; -1.87	0.07	0.70
<i>Total score</i>	92.33 (8.97)	93.26 (11.27)	-4.71; -2.85	0.05	0.80
Cognition skill	91.57 (9.50)	91.52 (9.30)	-3.53; -3.62	0.03	0.88
Motor skill	93.58 (12.17)	94.39 (11.97)	-5.40; -3.78	0.05	0.77

¹ 95% confidence interval for mean differences.

² Cohen's *d* for mean differences.

³ *p*-value for mean differences adjusted for GA and medical diagnosis.

Note. Mean (standard deviation).